

Access DB# 119453

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: NUDET Examiner #: 79501 Date: 4/15/04
 Art Unit: 164 Phone Number 30 Serial Number: 107076436
 Mail Box and Bldg/Room Location: REM 3000 Results Format Preferred (circle): PAPER DISK E-MAIL
 REF 3811

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

Earliest Priority Filing Date: (8/22/96)

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Rease search

1) 3 compound CLAIM 30 (100% - This can be searched by
Low A-Acid structure, if free of art
can cease further searching, but some
small may be (let out there), attached to
2nd Search to find structure w/ either
ABG & CLAIM 31 - if free of art, no
more searching needed
3rd If not on 1st step, search begins!
w/ any of APC's of CLAIM 32.

21 investor search

Tx Beverly, MARY

STAFF USE ONLY

Searcher: Beverly C 2528

Searcher Phone #: _____

Searcher Location: _____

Date Searcher Picked Up: _____

Date Completed: 04-15-04

Searcher Prep & Review Time: _____

Clerical Prep Time: _____

Online Time: _____

Type of Search

NA Sequence (#)

AA Sequence (#)

Structure (#) _____

Bibliographic

Litigation

Fulltext

Patent Family _____

Other _____

Vendors and cost where applicable

STN ✓

Dialog

Questel/Orbit

Dr. Link

Lexis/Nexis

Sequence Systems

WWW/Internet _____

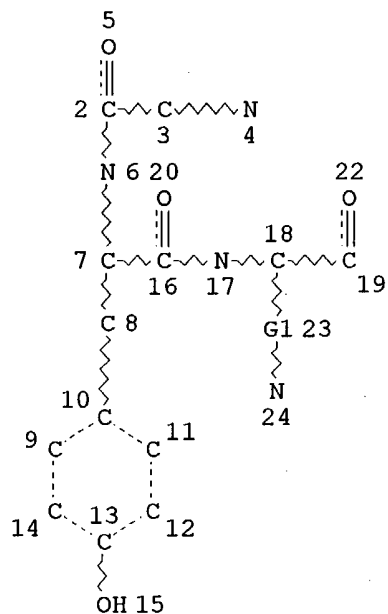
Other (specify) _____

Audet, M.
10/686436

10/686436

(FILE 'REGISTRY' ENTERED AT 09:00:42 ON 15 APR 2004)

L1 STR



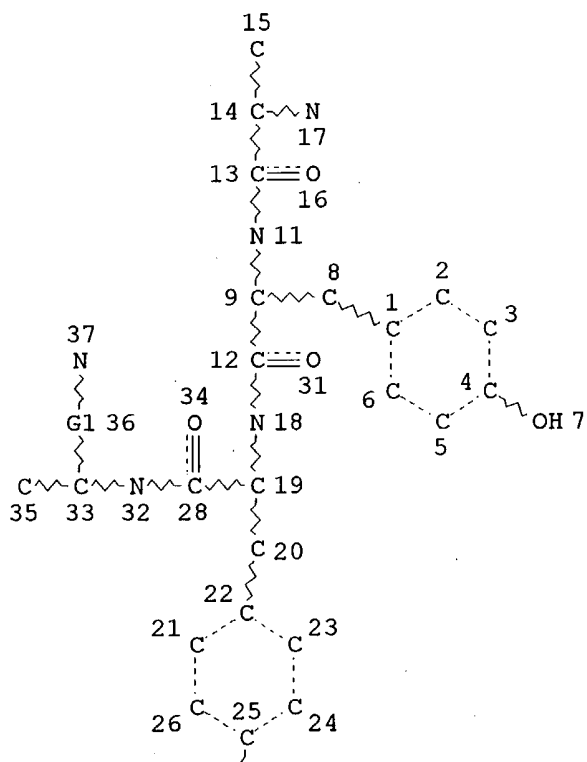
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L2 STR

10/686436



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Page 2-A

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

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NUMBER OF NODES IS 34

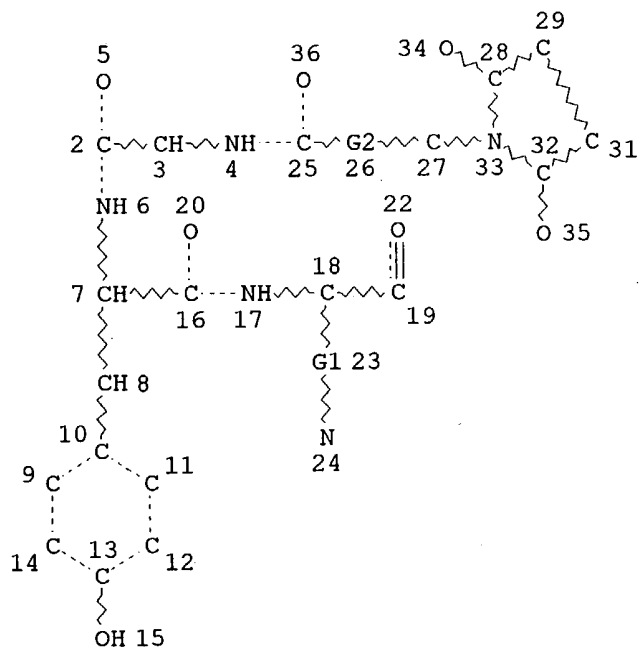
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L4 STR

Temp saved 7 days

10/686436



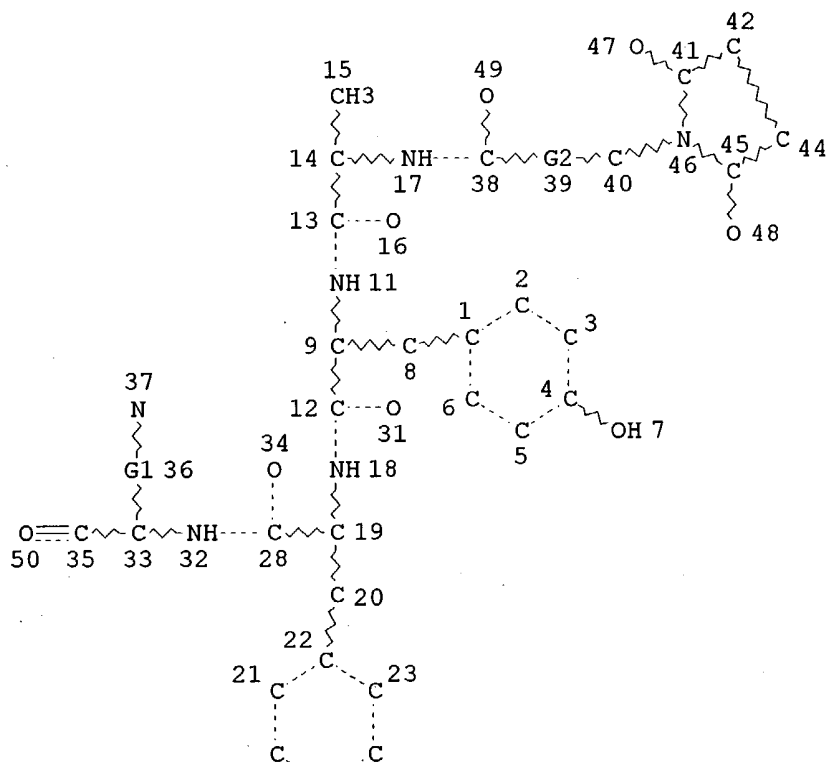
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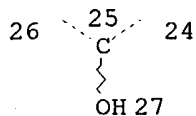
STEREO ATTRIBUTES: NONE
L5 5 SEA FILE=REGISTRY SUB=L3 SSS FUL L4
L6 STR

10/686436



Strs. 142

Page 1-A



Page 2-A

REP G1=(4-4) CH2

REP G2=(0-1) CB

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 46

STEREO ATTRIBUTES: NONE

L7 1 SEA FILE=REGISTRY SUB=L3 SSS FUL L6

L8 6 SEA FILE=REGISTRY ABB=ON PLU=ON L5 OR L7

FILE 'HCAPLUS' ENTERED AT 09:35:13 ON 15 APR 2004

L9 7 S L8

L9 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

Searcher : Shears 571-272-2528

10/686436

ACCESSION NUMBER: 2003:980784 HCAPLUS
DOCUMENT NUMBER: 140:47476
TITLE: Stable radioiodine conjugates and methods for
their synthesis
INVENTOR(S): Govindan, Serengulam V.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S., 13 pp., Cont.-in-part of U.S. 6,558,669.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6663866	B1	20031216	US 2000-605873	20000629
US 6558669	B1	20030506	US 1997-919477	19970828
EP 1219307	A2	20020703	EP 2002-75560	19971219
EP 1219307	A3	20040121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
WO 2002002150	A2	20020110	WO 2001-US20764	20010629
WO 2002002150	C1	20030116		
WO 2002002150	A3	20020906		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1299129	A2	20030409	EP 2001-950673	20010629
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003220470	A1	20031127	US 2003-359276	20030206
US 2004018148	A1	20040129	US 2003-395718	20030325
US 2004022725	A1	20040205	US 2003-411370	20030411

PRIORITY APPLN. INFO.:

US 1996-24738P P 19960828
US 1997-919477 A2 19970828
WO 1997-US14998 A 19970827
EP 1997-954212 A3 19971219
WO 1997-US23711 A 19971219
US 2000-605873 A 20000629
US 2000-696740 A2 20001026
WO 2001-US20764 W 20010629

AB Methods are described for conjugating radioiodinated peptides to non-metabolizable carbohydrates with improved yields and qualities of conjugates. Radioiodinated residualizing antibody conjugates comprising a carbohydrate-appended peptide are also provided. The instant radioiodinated residualizing antibody conjugates are particularly stable in vivo and are suitable for radioimmuno-detection and radioimmunotherapy of tumors.

IT 634907-72-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);

Searcher : Shears 571-272-2528

10/686436

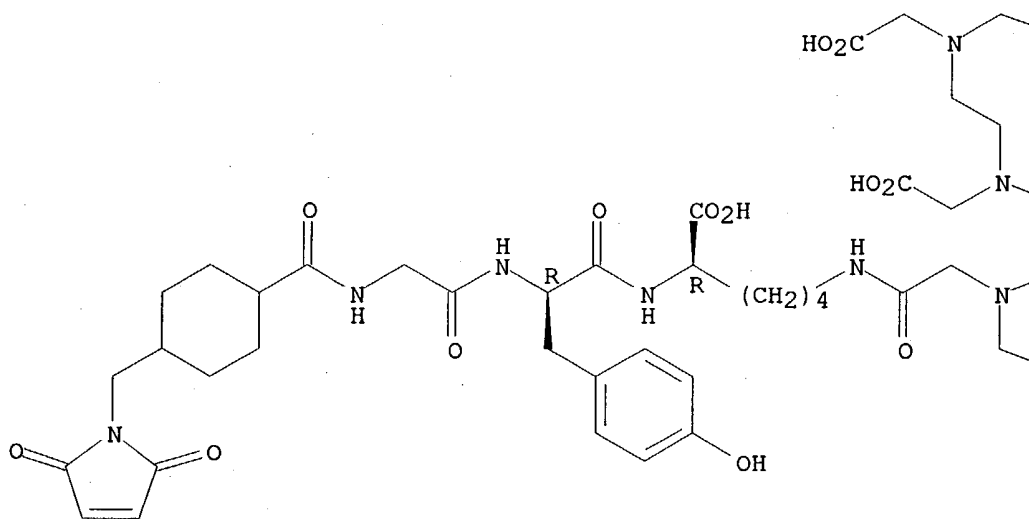
RACT (Reactant or reagent)
(radioiodinated antibody conjugates)

RN 634907-72-5 HCAPLUS

CN D-Lysine, N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]glycyl-D-tyrosyl-N6-[N-[2-[[2-bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]-1-[4-isothiocyanatophenyl)methyl]ethyl]-N-(carboxymethyl)glycyl]- (9CI)
(CA INDEX NAME)

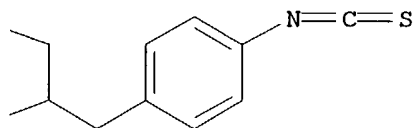
Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

CO2H



CO2H

REFERENCE COUNT:

19

THERE ARE 19 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

Searcher : Shears 571-272-2528

10/686436

L9 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:719518 HCAPLUS
DOCUMENT NUMBER: 139:259962
TITLE: Humanized murine anti-epithelial glycoprotein 1
(EGP-1) antibodies RS7 and conjugates for
diagnosis and treatment of cancer
INVENTOR(S): Govindan, Serengulam; Qu, Zhengxing; Hansen,
Hans J.; Goldenberg, David M.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA; McCall, John Douglas
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003074566	A2	20030912	WO 2003-GB885	20030303
WO 2003074566	A3	20040304		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

US 2004001825 A1 20040101 US 2003-377121 20030303

PRIORITY APPLN. INFO.: US 2002-360229P P 20020301

AB This invention relates to monovalent and multivalent, monospecific binding proteins and to multivalent, multispecific binding proteins. One embodiment of these binding proteins has one or more binding sites where each binding site binds with a target antigen or an epitope on a target antigen. Another embodiment of these binding proteins has two or more binding sites where each binding site has affinity towards different epitopes on a target antigen or has affinity towards either a target antigen or a hapten. The present invention further relates to recombinant vectors useful for the expression of these functional binding proteins in a host. More specifically, the present invention relates to the tumor-associated antigen binding protein designated RS7, and other EGP-1 binding-proteins. The invention further relates to humanized, human and chimeric RS7 antigen binding proteins, and the use of such binding proteins in diagnosis and therapy.

IT 588709-17-5D, antibody conjugates

RL: BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(humanized murine anti-EGP-1 antibodies RS7 and conjugates for diagnosis and treatment of cancer)

RN 588709-17-5 HCAPLUS

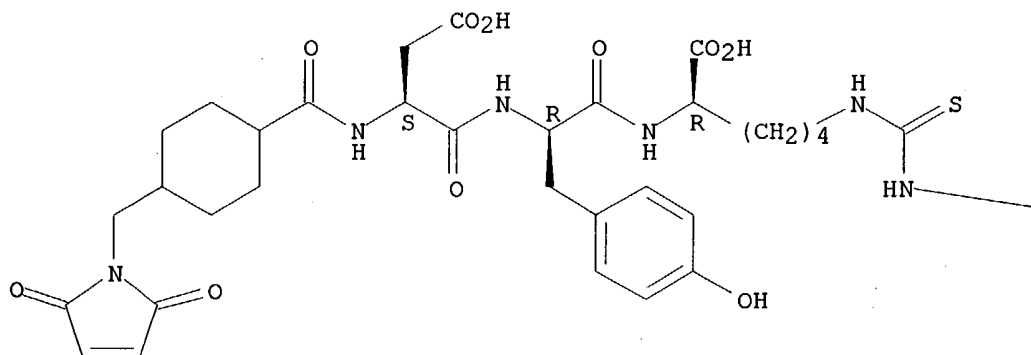
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Searcher : Shears 571-272-2528

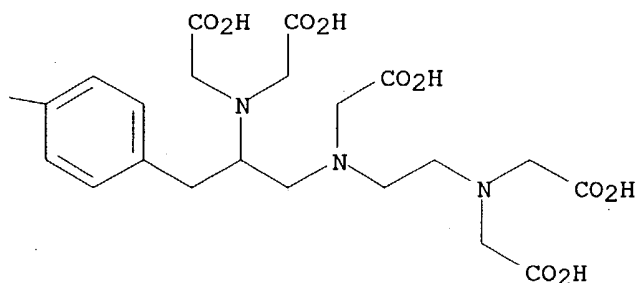
yl)methyl]cyclohexyl]carbonyl]-L- α -aspartyl-D-tyrosyl-N6-[[[4-[2-[bis(carboxymethyl)amino]-3-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]propyl]phenyl]amino]thioxomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L9 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:39624 HCAPLUS
 DOCUMENT NUMBER: 139:210070
 TITLE: Improved Iodine Radiolabels for Monoclonal Antibody Therapy
 AUTHOR(S): Stein, Rhona; Govindan, Serengulam V.; Mattes, M. Jules; Chen, Susan; Reed, Linda; Newsome, Guy; McBride, Bill J.; Griffiths, Gary L.; Hansen, Hans J.; Goldenberg, David M.
 CORPORATE SOURCE: Garden State Cancer Center, Belleville, NJ, 07109, USA
 SOURCE: Cancer Research (2003), 63(1), 111-118

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB A major disadvantage of ¹³¹I-labeled monoclonal antibodies (MAbs) for radioimmunotherapy has been the rapid diffusion of iodotyrosine from target cells after internalization and catabolism of the radioiodinated MAbs. We recently reported that a radioiodinated, diethylenetriaminepentaacetic acid-appended peptide, designated immunomedics' residualizing peptide 1 (IMP-R1), was a residualizing iodine label that overcame many of the limitations that had impeded the development of residualizing iodine for clin. use. To determine the factors governing the therapeutic index of the labeled MAb, as well as the factors required for production of radioiodinated MAb in high yield and with high specific activity, variations in the peptide structure of IMP-R1 were evaluated. A series of radioiodinated, diethylenetriaminepentaacetic acid-appended peptide moieties (IMP-R1 through IMP-R8) that differed in overall hydrophilicity and charge were compared. Radioiodinations of the peptides followed by conjugations to disulfide-reduced RS7 (an anti-epithelial glycoprotein-1 MAb) furnished radioimmunoconjugates in good overall incorporations, with immunoreactivities comparable to that of directly radioiodinated RS7. Specific activities of up to 8 mCi/mg and yields > 80% have been achieved. In vitro processing expts. showed marked increases in radioiodine retention with all of the adducts; radioiodine retention at 45 h was up to 86% greater in cells than with directly iodinated RS7. Each of the ¹²⁵I-peptide-RS7 conjugates was compared with ¹³¹I-RS7 (labeled by the chloramine-T method) in paired-label biodistribution studies in nude mice bearing human lung tumor xenografts. All of the residualizing substrates exhibited significantly enhanced retention in tumor in comparison to directly radioiodinated RS7, but the nontarget uptakes differed significantly among the residualizing labels. The best labels were IMP-R4 and IMP-R8, showing superior tumor-to-non-tumor ratios by virtue of high tumor uptake and retention and low normal organ uptake, as well as superior radiochem. properties. The therapeutic efficacy of ¹³¹I-IMP-R4-RS7 was compared with that of conventionally ¹³¹I-labeled RS7 and ⁹⁰yttrium-RS7 in the nude mice lung cancer model. The therapeutic efficacy of ¹³¹I-IMP-R4-RS7 and ⁹⁰yttrium-RS7 were equivalent, and both agents yielded significantly improved control of tumor growth compared with conventional ¹³¹I-labeled RS7.

IT 588706-62-1DP, ¹²⁵I-labeled MAb conjugates
 588709-17-5DP, ¹²⁵I-labeled MAb conjugates
 RL: PKT (Pharmacokinetics); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

(¹²⁵I-labeled IMP-R (immunomedics residualizing peptides)-MAb RS7
 conjugates for cancer radioimmunotherapy)

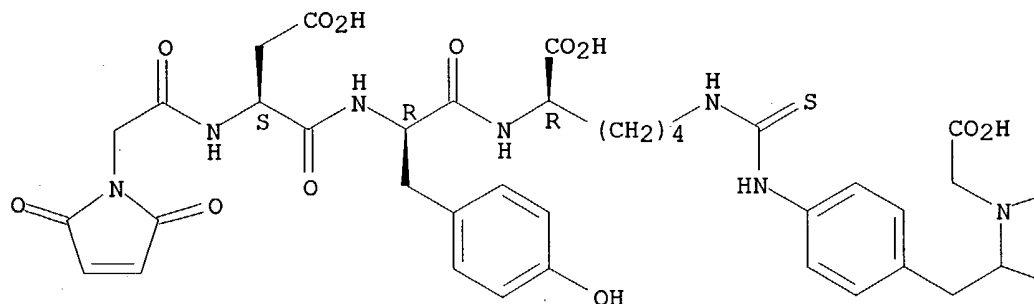
RN 588706-62-1 HCAPLUS

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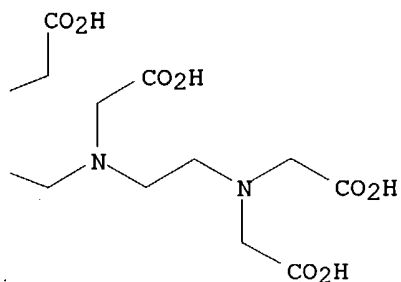
10/686436

Absolute stereochemistry.

PAGE 1-A



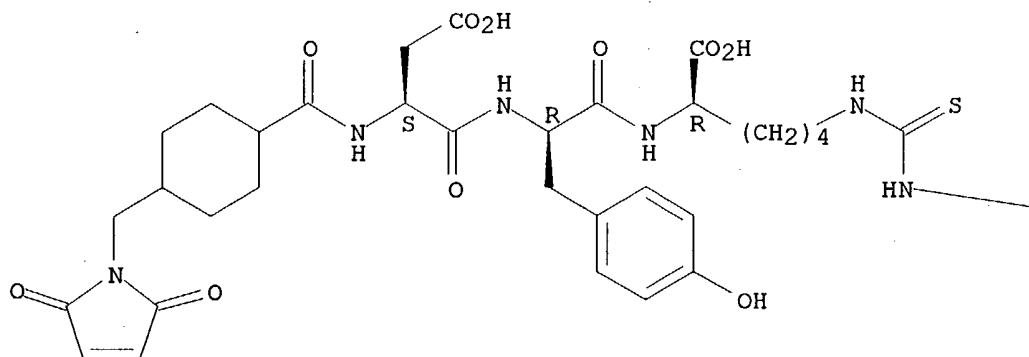
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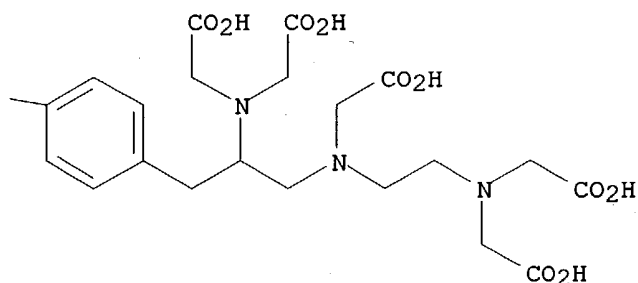
RN 588709-17-5 HCAPLUS
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

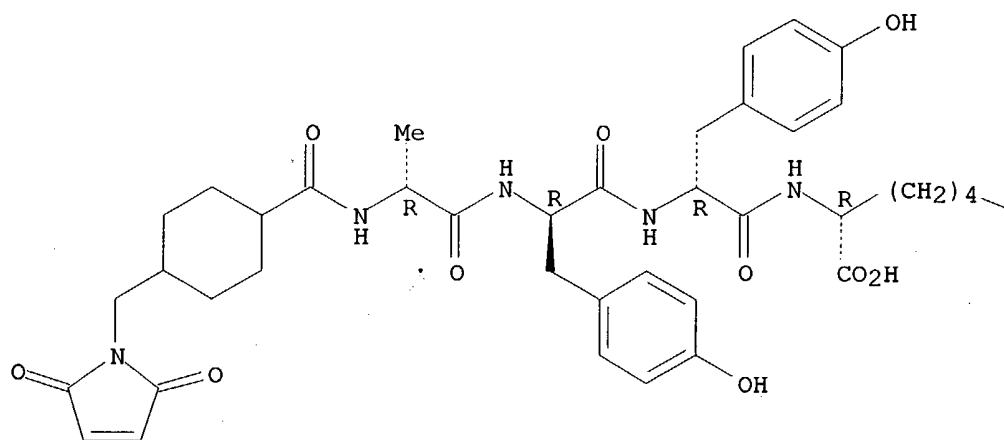


IT 224045-69-6D, 125I-labeled MAb conjugates
 261516-54-5D, 125I-labeled MAb conjugates
 RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (125I-labeled IMP-R (immunomedics residualizing peptides)-MAb RS7 conjugates for cancer radioimmunotherapy)
 RN 224045-69-6 HCAPLUS
 CN D-Lysine, 1',1'''-[[[(carboxymethyl)imino]di-2,1-ethanediyl]bis[N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]-D-alanyl-D-tyrosyl-D-tyrosyl-N6-[N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)]

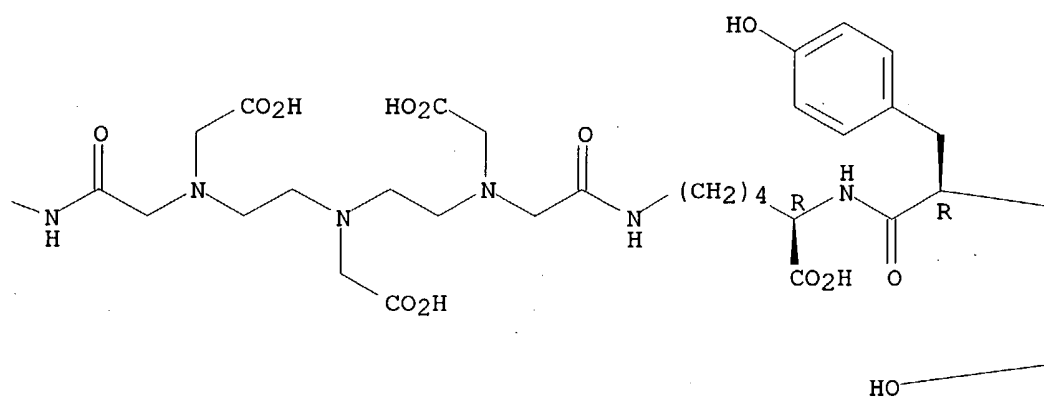
Absolute stereochemistry.

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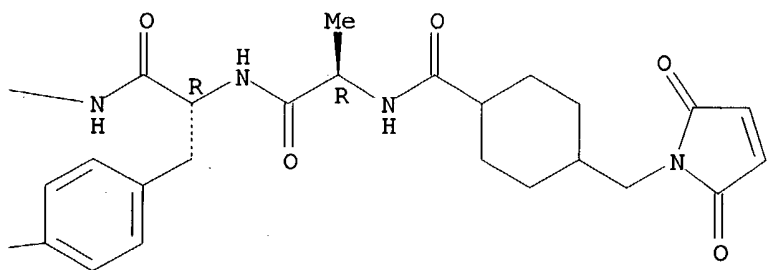


PAGE 1-B



10/686436

PAGE 1-C

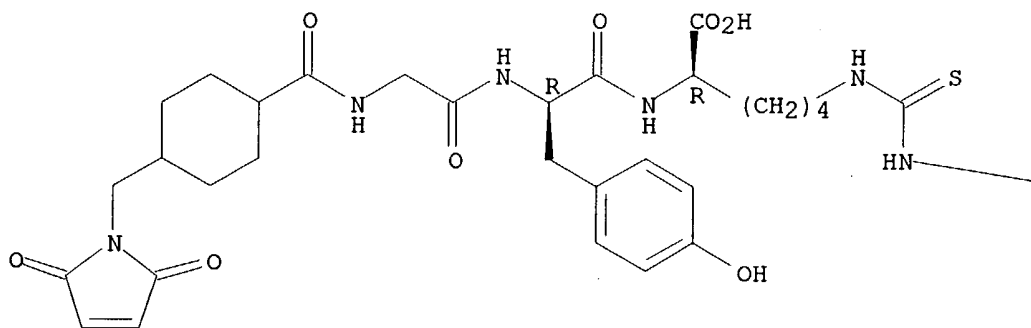


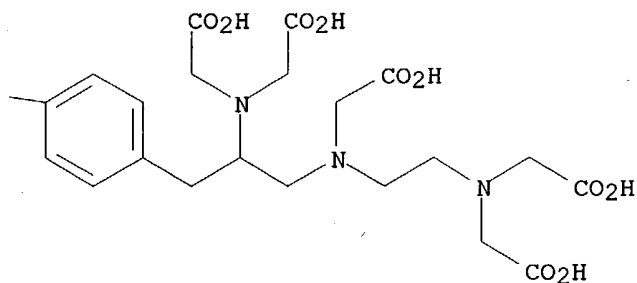
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Absolute stereochemistry.

PAGE 1-A





REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 7 HCAPLUS ~~COPYRIGHT~~ 2004 ACS on STN

ACCESSION NUMBER: 2001:697382 HCAPLUS

DOCUMENT NUMBER: 136:275439

TITLE: Radioimmunotherapy of a human lung cancer xenograft with monoclonal antibody RS7: Evaluation of ¹⁷⁷Lu and comparison of its efficacy with that of ⁹⁰Y and residualizing ¹³¹I

AUTHOR(S): Stein, Rhona; Govindan, Serengulam V.; Chen, Susan; Reed, Linda; Richel, Heidi; Griffiths, Gary L.; Hansen, Hans J.; Goldenberg, David M.
CORPORATE SOURCE: Garden State Cancer Center, Belleville, NJ, 07109, USA

SOURCE: Journal of Nuclear Medicine (2001), 42(6), 967-974

CODEN: JNMEAQ; ISSN: 0161-5505

PUBLISHER: Society of Nuclear Medicine

DOCUMENT TYPE: Journal

LANGUAGE: English

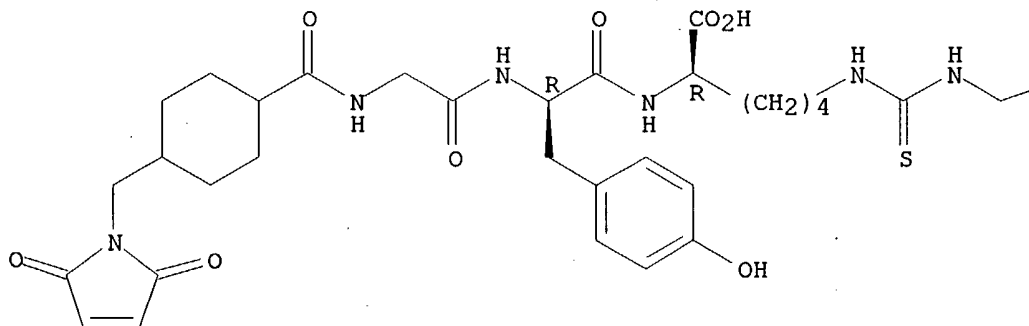
AB Tumor targeting and therapeutic efficacy of ¹⁷⁷Lu-labeled monoclonal antibody (mAb) RS7 (antiepithelial glycoprotein-1) was evaluated in a human nonsmall cell lung carcinoma xenograft model. The potential of ¹⁷⁷Lu-labeled RS7 was compared with that of RS7 labeled with ⁹⁰Y and a residualizing form of ¹³¹I. A 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) conjugate of RS7 was used for radiolabeling with ¹⁷⁷Lu-acetate or ^{88/90}Y-acetate. Biodistribution and therapy studies were conducted in nude mice with s.c. Calu-3 xenografts. Therapy studies were performed using the maximal tolerated doses (MTDs) of ⁹⁰Y-DOTA-RS7 (3.9 MBq [105 \geq Ci]) and ¹⁷⁷Lu-DOTA-RS7 (10.2 MBq [275 \geq Ci]) and compared with the data obtained using the MTD (13.0 MBq [350 μ Ci]) of a residualizing form of ¹³¹I-RS7. Radiolabeling of RS7-DOTA conjugate with ¹⁷⁷Lu-acetate was facile. ¹⁷⁷Lu-DOTA-RS7 displayed biodistribution results that were nearly identical to that of the ⁸⁸Y analog in a paired-label study. The mean percentage injected doses per g (%ID/g) for ¹⁷⁷Lu-RS7 and ⁸⁸Y-RS7 (in parentheses) in

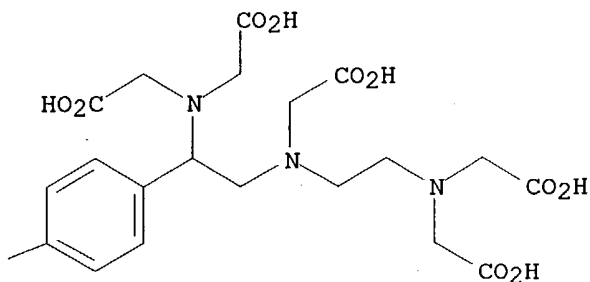
tumor were 38.3 %ID/g (39.1 %ID/g), 63.0 %ID/g (66.0 %ID/g), 63.0 %ID/g (65.8 %ID/g), and 34.0 %ID/g (34.9 %ID/g) on days 1, 3, 7, and 14, resp. Elimination of established tumors, with an initial mean tumor volume of 0.24 cm³, was shown using doses of ¹⁷⁷Lu-DOTA-RS7 ranging from 5.6 to 9.3 MBq (150-250 µCi) per nude mouse, with no significant difference in response rate noted between the doses in this range. Specificity of the therapeutic effect was shown in an isotype-matched control experiment, in which ¹⁷⁷Lu-DOTA-RS7 was markedly more effective than the ¹⁷⁷Lu-DOTA control antibody. A comparison of the therapeutic efficacies of ¹⁷⁷Lu-DOTA-RS7 and ⁹⁰Y-DOTA-RS7, using mice with established tumors with an initial mean tumor volume of 0.85 cm³, indicated similar tumor growth inhibition and similar tumor regrowth profiles. The therapy data were similar to those obtained with residualizing ¹³¹I-RS7 obtained at the same time. ¹⁷⁷Lu-RS7 is an effective radioimmunoconjugate for radioimmunotherapy. With its radiophys. properties similar to those of ¹³¹I, coupled with its facile and stable attachment to mAb, ¹⁷⁷Lu promises to be an alternative to ¹³¹I, and a complement to ⁹⁰Y, in radioimmunotherapy.

IT **224045-67-4D**, IMP-R 1, ¹³¹I-labeled antibody conjugate
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (radioimmunotherapy of lung cancer with ¹⁷⁷Lu-labeled monoclonal antibody RS7: comparison with ⁹⁰Y and residualizing ¹³¹I)
 RN 224045-67-4 HCAPLUS
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Absolute stereochemistry.

PAGE 1-A





REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 7 HCAPLUS- COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1999:740238 HCAPLUS
 DOCUMENT NUMBER: 132:218942
 TITLE: Targeting human cancer xenografts with monoclonal antibodies labeled using radioiodinated, diethylenetriaminepentaacetic acid-appended peptides
 AUTHOR(S): Stein, Rhona; Govindan, Serengulam V.; Jules, Mattes, M.; Shih, Lisa B.; Griffiths, Gary L.; Hansen, Hans J.; Goldenberg, David M.
 CORPORATE SOURCE: Garden State Cancer Center, Belleville, NJ, 07109, USA
 SOURCE: Clinical Cancer Research (1999), 5(10, Suppl.), 3079s-3087s
 CODEN: CCREF4; ISSN: 1078-0432
 PUBLISHER: American Association for Cancer Research
 DOCUMENT TYPE: Journal
 LANGUAGE: English

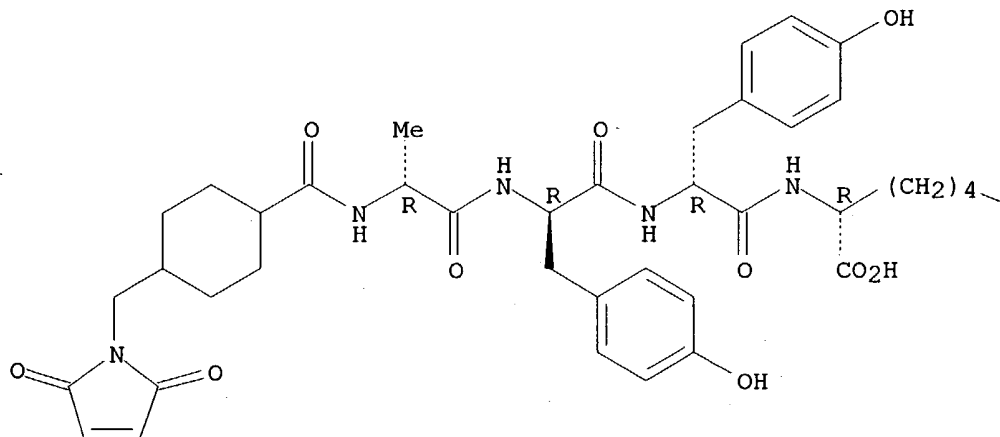
AB A new nonmetabolizable peptide approach to the production of residualizing radioiodine was evaluated in nude mice bearing xenografts of human lung adenocarcinoma (Calu-3) and B-cell lymphoma (Ramos). Monoclonal antibodies (MAbs) RS7 (anti-epithelial glycoprotein-1) and LL2 (anti-CD22) were radioiodinated using the thiol-reactive diethylenetriaminepentaacetic acid-D-peptide adducts IMP-R1 and IMP-R2. 125I-IMP-R1- and 125I-IMP-R2-labeled MAbs were compared to the MAbs iodinated by the conventional chloramine-T approach, 111In, and 131I-dilactitoltyramine (DLT). In vivo biodistribution studies demonstrated a significant improvement in the tumor accretion of radiolabel using the 125I-IMP-R1 labeled MAbs compared with the conventionally iodinated antibodies. For example, at day 7, the percentage of injected dose per g of tissue in Calu-3 was $7.9 \pm 4.1\%$ and $18.1 \pm 7.9\%$ ($P < 0.05$) for the conventional 131I- and 125I-IMP-R1-RS7, resp., and tumor:nontumor ratios were 2.6-4.5-fold higher with the 125I-IMP-R1-RS7. It is estimated that 131I-IMP-R1-RS7 would deliver a dose to tumor (at the estimated maximum tolerated dose) 3.9 times greater than conventional 131I-labeled RS7, 1.4 times greater than 90Y-labeled RS7, and 0.7 times that of 131I-DLT-labeled RS7. Tumor accretion of 125I-IMP-R2-RS7 was also

improved compared with conventionally iodinated antibody. However, this label also caused a large increase in kidney accretion. Similar improvements in tumor accretion and tumor:nontumor ratios were observed when ^{125}I -IMP-R1-LL2 was used in the Ramos model. IMP-R1 offers a practical and useful residualizing radioiodine label because labeling efficiency is at least 10 times greater than that of the residualizing label DLT, without MAb aggregation. Structural modifications can be envisioned for further improvements in radioiodine incorporation, specific activity, and tumor dosimetry, and efforts along these lines are under way.

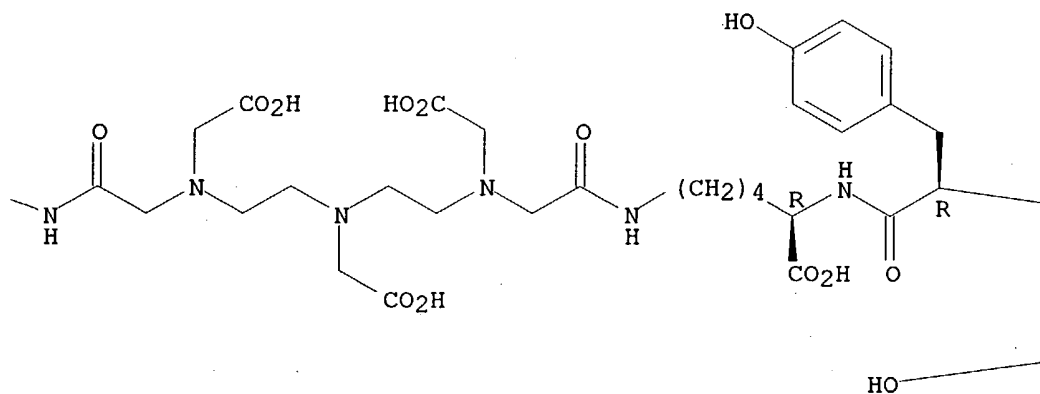
- IT **224045-69-6D**, radiolabeled monoclonal antibody conjugates
261516-54-5D, radiolabeled monoclonal antibody conjugates
 RL: BPR (Biological process); BSU (Biological study, unclassified);
 BIOL (Biological study); PROC (Process)
 (targeting human cancer xenografts with monoclonal antibodies
 labeled using radioiodinated, diethylenetriaminepentaacetic
 acid-appended peptides)
- RN 224045-69-6 HCAPLUS
- CN D-Lysine, 1',1'''-[[[(carboxymethyl)imino]di-2,1-ethanediyl]bis[N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]-D-alanyl-D-tyrosyl-D-tyrosyl-N6-[N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

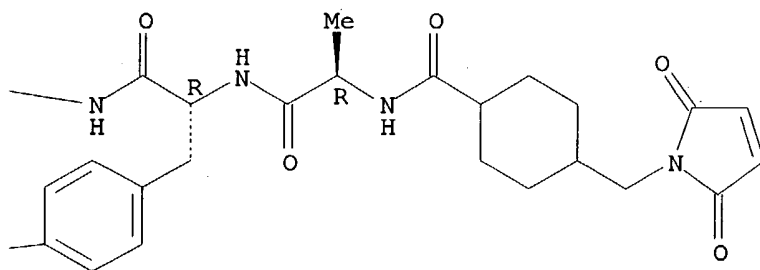
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PAGE 1-B



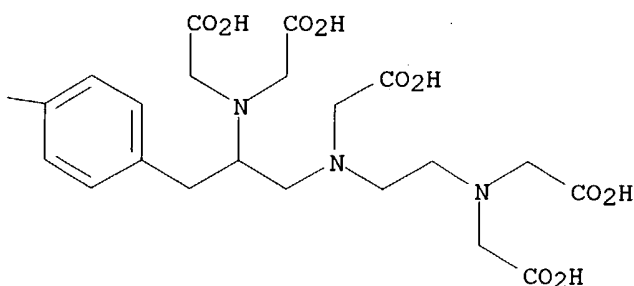
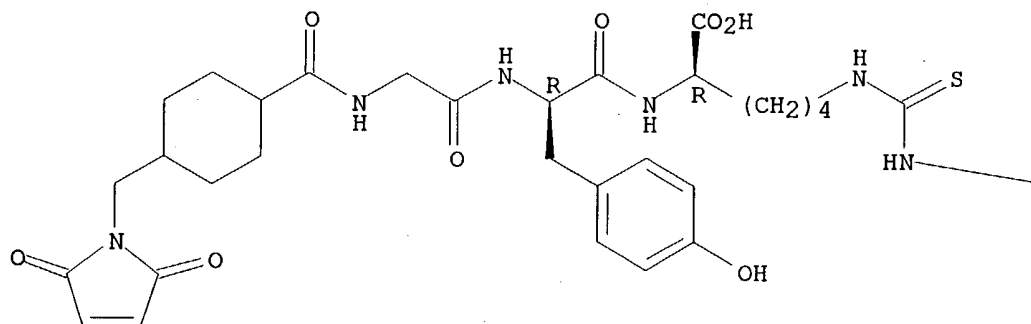
PAGE 1-C



RN 261516-54-5 HCAPLUS

CN D-Lysine, N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]glycyl-D-tyrosyl-N6-[[[4-[2-[bis(carboxymethyl)amino]-3-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]propyl]phenyl]amino]thioxomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999-402525 HCAPLUS

DOCUMENT NUMBER: 131:211044

TITLE: Cytotoxicity with Auger electron-emitting radionuclides delivered by antibodies

AUTHOR(S): Griffiths, Gary L.; Govindan, Serengulam V.; Sgouros, George; Ong, Gaik Lin; Goldenberg, David M.; Mattes, M. Jules

CORPORATE SOURCE: Immunomedics, Inc., Morris Plains, NJ, USA

SOURCE: International Journal of Cancer (1999), 81(6), 985-992

CODEN: IJCNAW; ISSN: 0020-7136

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We investigated the in vitro cytotoxic potential of Auger electron-emitting radionuclides delivered to the cytoplasm or, more

specifically, to lysosomes, via antibodies. The antibody (Ab) used was LLI, which is specific for CD74, an epitope of the major histocompatibility complex (MHC) class II antigen invariant chain, II, present on the cell surface. It is taken up in large amts., approx. 107 Ab mols. per cell per day, and delivered to lysosomes. The radioisotopes tested included ^{111}In , $^{99\text{m}}\text{Tc}$ and ^{125}I . With sufficient specific activity, approx. 10 mCi/mg Ab, all of these isotopes were potent cytotoxic agents. ^{125}I was active only if a "residualizing" form was used, meaning a form that is trapped within cells after catabolism of the Ab to which it was conjugated (conventional oxidative iodination produces a non-residualizing label). The conjugates of ^{111}In and $^{99\text{m}}\text{Tc}$ used are known to be residualizing. One hundred percent cell kill in vitro was obtained with ^{111}In and ^{125}I , under conditions in which a non-reactive control Ab, conjugated in the same way, produced no significant toxicity. $^{99\text{m}}\text{Tc}$ was also potent and specific, but appeared somewhat less active than the other isotopes under the conditions evaluated. Although few Abs are accreted by cells at the same rate as LLI, it may be possible to use other Abs to deliver similar amts. of radioactivity, if Abs with higher specific activity can be produced. Such conjugated radioisotopes may be useful for attacking tumor cells in vivo, particularly for single cells or micrometastases.

IT 224045-69-6D, radiolabeled antibody conjugates

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

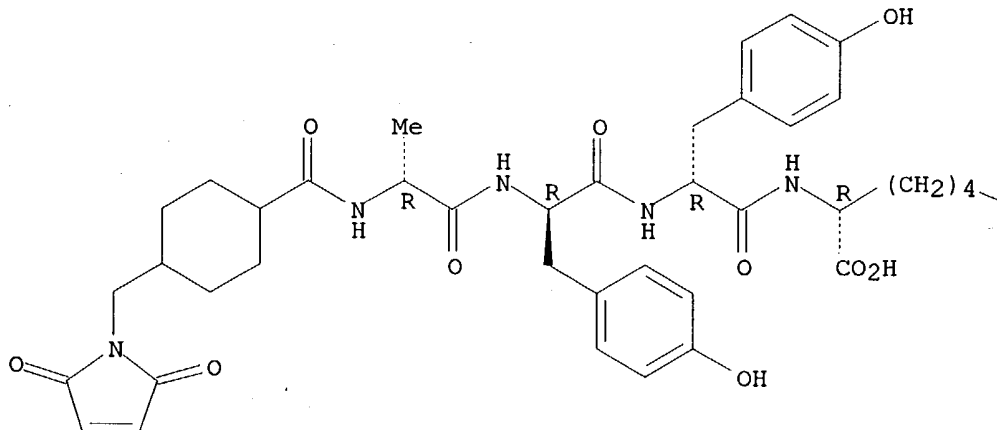
(cytotoxicity with Auger electron-emitting radionuclides delivered by antibodies)

RN 224045-69-6 HCAPLUS

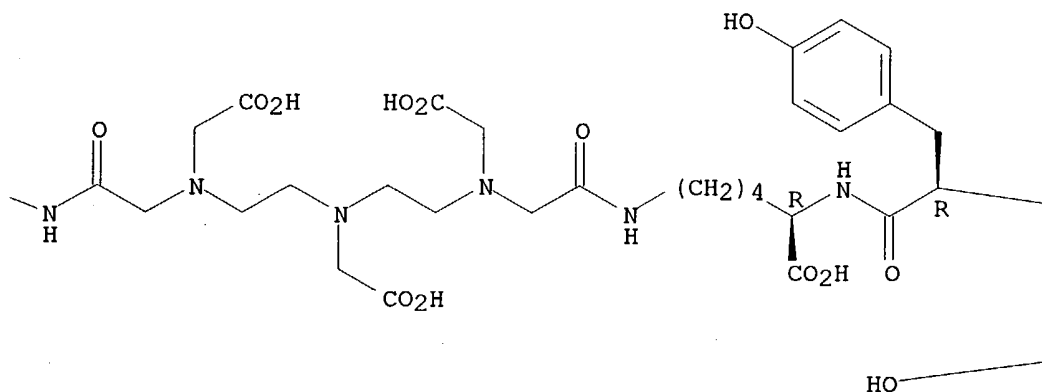
CN D-Lysine, 1',1'''-[[[(carboxymethyl)imino]di-2,1-ethanediyl]bis[N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]-D-alanyl-D-tyrosyl-D-tyrosyl-N6-[N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

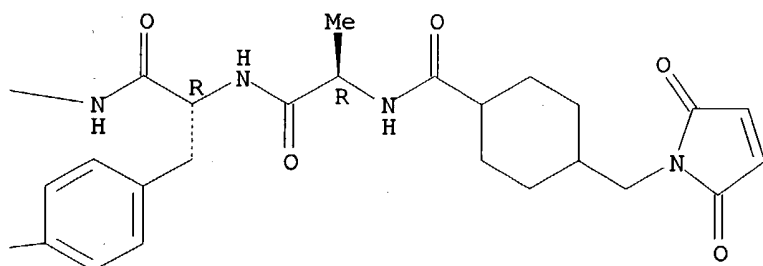
PAGE 1-A



PAGE 1-B



PAGE 1-C



REFERENCE COUNT:

27

THERE ARE 27 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L9 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:90010 HCAPLUS

DOCUMENT NUMBER: 130:334689

TITLE:

Labeling of Monoclonal Antibodies with
Diethylenetriaminepentaacetic Acid-Appended
Radioiodinated Peptides Containing D-Amino Acids
Govindan, Serengulam V.; Mattes, M. Jules;
Stein, Rhona; McBride, Bill J.; Karacay, Habibe;
Goldenberg, David M.; Hansen, Hans J.;
Griffiths, Gary L.

AUTHOR(S):

CORPORATE SOURCE:

Immunomedics Inc., Morris Plains, NJ, 07950, USA
Bioconjugate Chemistry (1999), 10(2), 231-240

SOURCE:

Searcher : Shears 571-272-2528

PUBLISHER: CODEN: BCCHE; ISSN: 1043-1802
 American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English

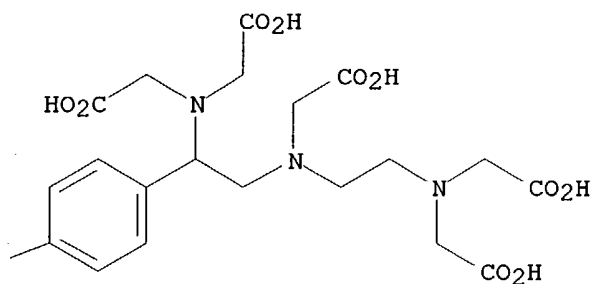
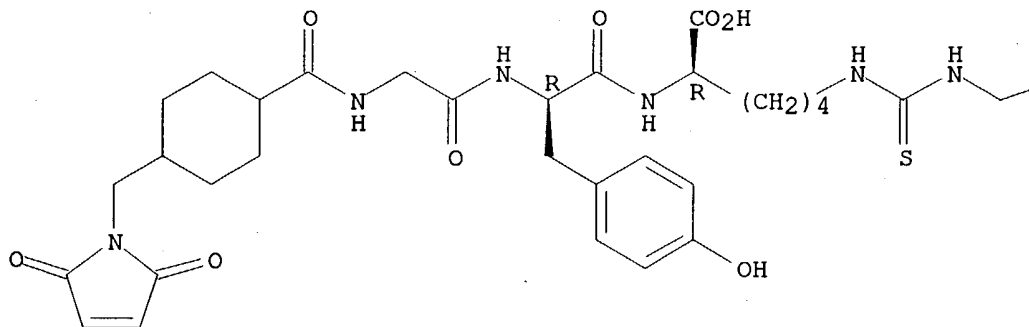
AB The optimal use of radioiodinated internalizing monoclonal antibodies (mAbs) for radio-immunotherapy necessitates the development of practical methods for increasing the level of retention of ¹³¹I in the tumor. Lysosomally trapped ("residualizing") iodine radiolabels that have been previously designed are based mostly on carbohydrate-tyramine adducts, but these methods have drawbacks of low overall yields and/or high levels of mAb aggregation. We have developed a method using thiol-reactive diethylenetriaminepentaacetic acid (DTPA)-peptide adducts wherein the peptides are assembled with one or more D-amino acids, including D-tyrosine. Two such substrates, R-Gly-D-Tyr-D-Lys[1-(p-thiocarbonylamino benzyl)DTPA], referred to as IMP-R1, and [R-D-Ala-D-Tyr-D-Tyr-D-Lys]2(CA-DTPA), referred to as IMP-R2, wherein R is 4-(N-maleimidomethyl)cyclohexane-1-carbonyl, were synthesized by preparing functional group-protected peptides on a solid phase, selectively derivatizing the lysine side chain with 1-(p-isothiocyanatobenzyl)DTPA or DTPA dianhydride (CA-DTPA), deprotecting other functional groups, and finally derivatizing the peptide's N-terminus so it contained a maleimide group. Radioiodinations of the peptides followed by conjugations to disulfide-reduced mAbs, carried out as a one-vial procedure, resulted in 32-89% overall yields, at specific activities of 1.8-11.1 mCi/mg, with less than 2% aggregation. Two internalizing mAbs, LL2 (anti-CD 22 B-cell lymphoma mAb) and RS7 (an anti-adenocarcinoma mAb which targets EGP-1 antigen), labeled with this procedure exhibited a 2-3-fold better cellular retention in Ramos and Calu-3 tumor cell lines, in vitro, resp., compared to the same mAbs radioiodinated with the chloramine-T method. The rationale for the new approach, syntheses, radiochem. and in vitro data are presented.

IT **224045-67-4P 224045-69-6P**
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
 RACT (Reactant or reagent)
 (intermediate; labeling of monoclonal antibodies with
 DTPA-appended radioiodinated peptides containing D-amino acids and
 tumor cell uptake)

RN 224045-67-4 HCAPLUS

CN D-Lysine, N-[[4-[(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)methyl]cyclohexyl]carbonyl]glycyl-D-tyrosyl-N6-[[[4-[1-bis(carboxymethyl)amino]-2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]phenyl]methyl]amino]thioxomethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

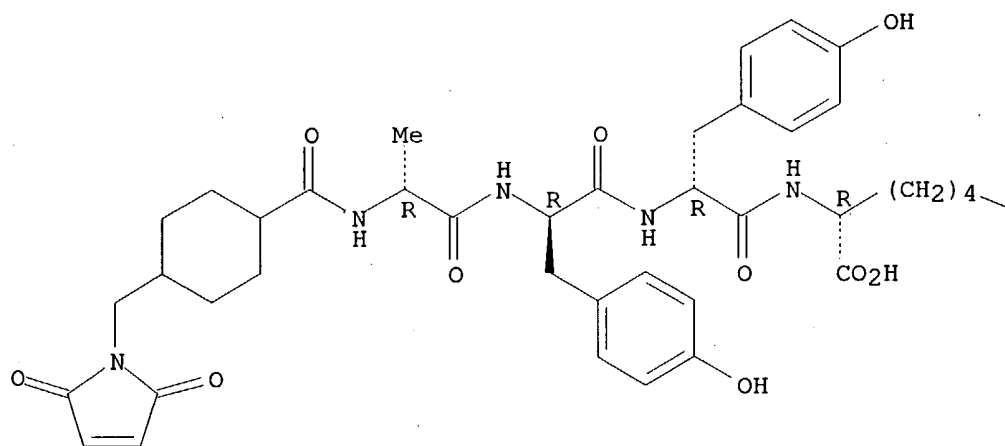


RN 224045-69-6 HCAPLUS

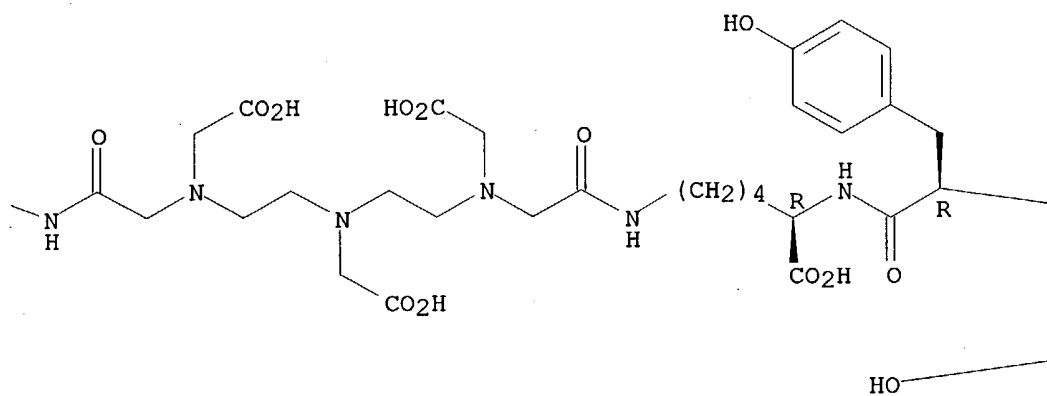
CN D-Lysine, 1',1'''-[[[(carboxymethyl)imino]di-2,1-ethanediyl]bis[N-[[4-
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 INDEX NAME)

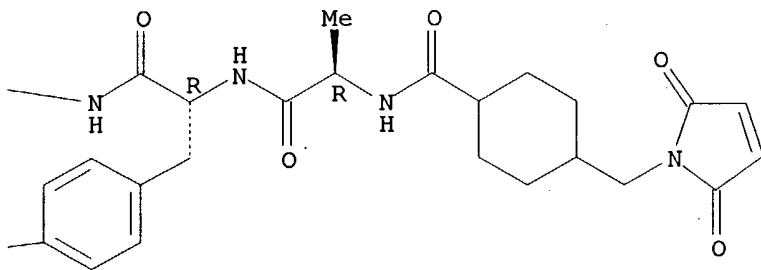
Absolute stereochemistry.

PAGE 1-A



PAGE 1-B





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L10 FILE 'CAOLD' ENTERED AT 09:36:32 ON 15 APR 2004
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L11 FILE 'USPATFULL' ENTERED AT 09:36:42 ON 15 APR 2004
2 S L8

L11 ANSWER 1 OF 2 USPATFULL on STN

ACCESSION NUMBER: 2004:1806 USPATFULL

TITLE: RS7 antibodies

INVENTOR(S): Govindan, Serengulam, Summit, NJ, UNITED STATES
Qu, Zhengxing, Warren, NJ, UNITED STATES
Hansen, Hans, Picayune, MS, UNITED STATES
Goldenberg, David, Mendham, NJ, UNITED STATES

PATENT ASSIGNEE(S): Immunomedics, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004001825	A1	20040101
APPLICATION INFO.:	US 2003-377121	A1	20030303 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-360229P	20020301 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	FOLEY AND LARDNER, SUITE 500, 3000 K STREET NW, WASHINGTON, DC, 20007	
NUMBER OF CLAIMS:	36	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	17 Drawing Page(s)	
LINE COUNT:	3417	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to monovalent and multivalent, monospecific
binding proteins and to multivalent, multispecific binding

10/686436

proteins. One embodiment of these binding proteins has one or more binding sites where each binding site binds with a target antigen or an epitope on a target antigen. Another embodiment of these binding proteins has two or more binding sites where each binding site has affinity towards different epitopes on a target antigen or has affinity towards either a target antigen or a hapten. The present invention further relates to recombinant vectors useful for the expression of these functional binding proteins in a host. More specifically, the present invention relates to the tumor-associated antigen binding protein designated RS7, and other EGP-1 binding-proteins. The invention further relates to humanized, human and chimeric RS7 antigen binding proteins, and the use of such binding proteins in diagnosis and therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 2 OF 2 USPATFULL on STN

ACCESSION NUMBER: 2003:326858 USPATFULL

TITLE: Stable radioiodine conjugates and methods for their synthesis

INVENTOR(S): Govindan, Serengulam V., Summit, NJ, United States

PATENT ASSIGNEE(S): Immunomedics, Inc., Morris Plains, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6663866	B1	20031216
APPLICATION INFO.:	US 2000-605873		20000629 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1997-919477, filed on 28 Aug 1997, now patented, Pat. No. US 6558669		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1996-24738P	19960828 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Celsa, Bennett	
LEGAL REPRESENTATIVE:	Foley & Lardner	
NUMBER OF CLAIMS:	14	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)	
LINE COUNT:	1180	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods are described for conjugating radioiodinated peptides to non-metabolizable carbohydrates with improved yields and qualities of conjugates. Radioiodinated residualizing antibody conjugates comprising a carbohydrate-appended peptide are also provided. The instant radioiodinated residualizing antibody conjugates are particularly stable in vivo and are suitable for radioimmunodetection and radioimmunotherapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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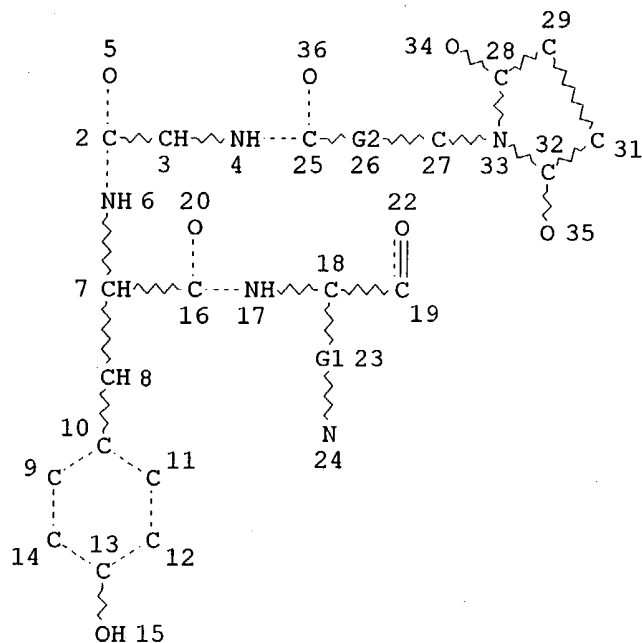
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ASPL

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L4

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REP G2=(0-1) CB

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RSPEC I

NUMBER OF NODES IS 33

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:

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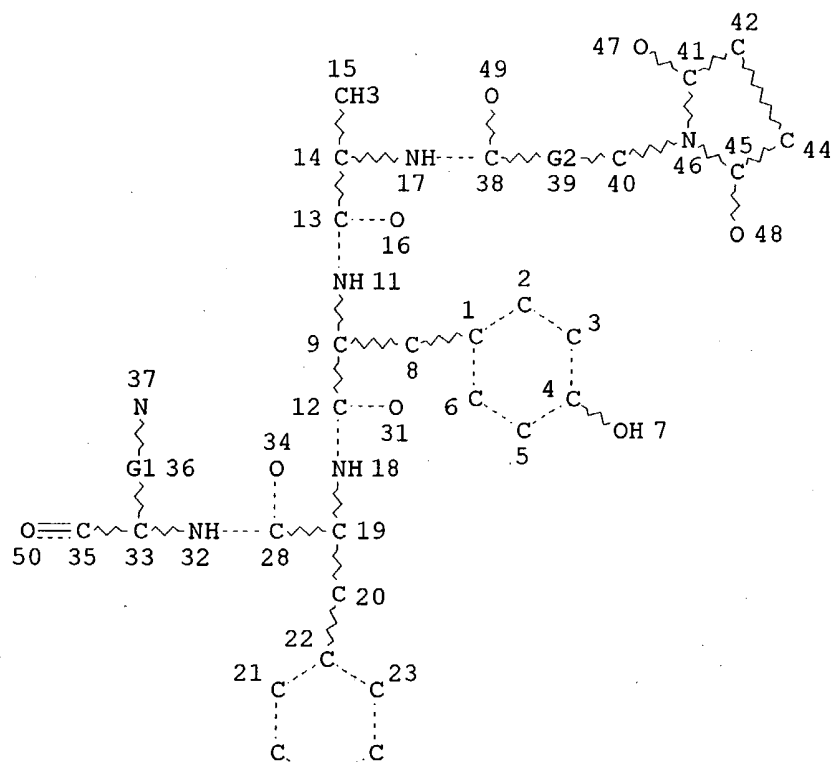
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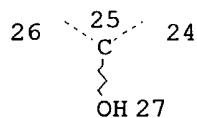
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Page 1-A



Page 2-A

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GRAPH ATTRIBUTES:

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STEREO ATTRIBUTES: NONE

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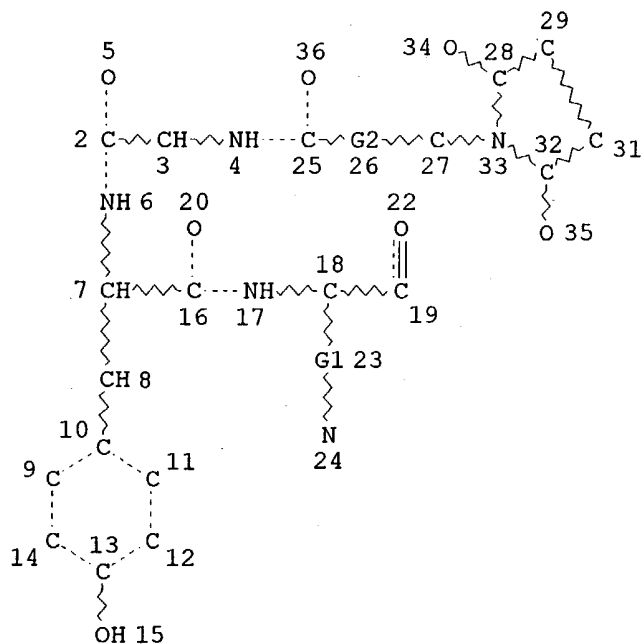
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS 33

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
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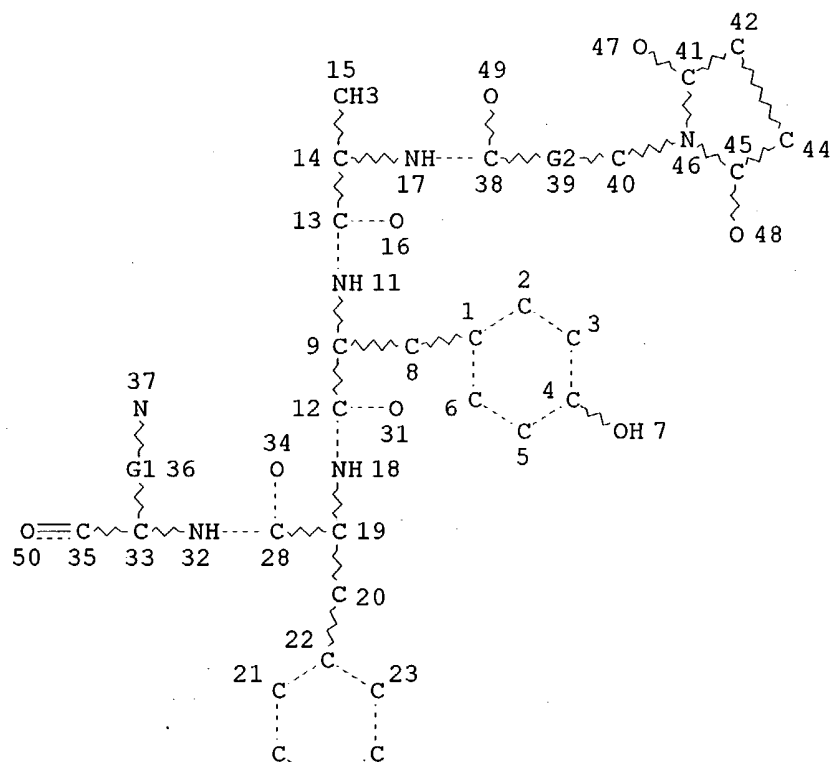
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0 ANSWERS

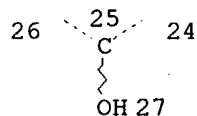
L6 STR

Searcher : Shears 571-272-2528

10/686436



Page 1-A



Page 2-A

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REP G2=(0-1) CB

NODE ATTRIBUTES:

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 46

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:

ECLEVEL IS LIM ON ALL NODES

ALL RING(S) ARE ISOLATED

L16

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Searcher : Shears 571-272-2528

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L19 160 S L17 AND L18
L20 3398 S L17 OR L18
L21 73 S (L19 OR L20) AND (RADIOIODIN? OR RADIO IODIN?)
L22 29 DUP REM L21 (44 DUPLICATES REMOVED)
L23 234 S RADIO I
L24 0 S (L19 OR L20) AND L23

- Author (s)

L22 ANSWER 1 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2004:175088 HCAPLUS

TITLE: Preclinical Therapy of Breast Cancer with a
Radioiodinated Humanized Anti-EGP-1
Monoclonal Antibody: Advantage of a
Residualizing Iodine Radiolabel

AUTHOR(S): **Govindan, Serengulam V.**; Stein, Rhona;
Qu, Zhengxing; Chen, Susan; Andrews, Philip; Ma,
Hong; Hansen, Hans J.; **Griffiths, Gary**
L.; Horak, Ivan D.; Goldenberg, David M.

CORPORATE SOURCE: Immunomedics, Inc.

SOURCE: Breast Cancer Research and Treatment (2004),
84(2), 173-182

CODEN: BCTRD6; ISSN: 0167-6806

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background. A humanized monoclonal antibody (MAb), hRS7, labeled with ¹³¹I-IMP-R4, was evaluated for the preclin. radioimmunotherapy (RAIT) of breast cancer. ¹³¹I-IMP-R4 is an improved residualizing form of ¹³¹I that overcomes the short tumor residence time associated with conventionally **radioiodinated** MABs. RS7, an internalizing MAb, recognizes epithelial glycoprotein-1, which is highly expressed in the carcinomas of breast, lung, ovary, and prostate. Methods. A humanized version of RS7 was generated by CDR-grafting and transfection. In vivo expts. were carried out in nude mice bearing s.c. MDA-MB-468 human breast cancer xenografts. Therapy expts. were performed using established tumors with mean tumor volume (MTV) of 0.3 cm³, and single administrations, at .apprx.70% of the estimated maximum tolerated doses (MTD), of the residualizing ¹³¹I-IMP-R4-hRS7 and ¹³¹I-hRS7 prepared by the conventional chloramine-T method [¹³¹I-hRS7 (CT)]. Therapeutic specificity was determined by comparison with untreated and non-specific MAB controls. Results. hRS7 was functionally very similar to murine and chimeric RS7. A biodistribution study using ¹²⁵I-IMP-R4-hRS7 and ¹³¹I-hRS7 (CT) indicated a dosimetric advantage for the former. The MTVs 8 wk post-treatment were 20, 163, and 280% of the starting MTVs of ¹³¹I-IMP-R4-hRS7-treated, ¹³¹I-hRS7 (CT)-treated, and untreated groups, resp. Complete remissions were seen in 5 of 11 [and 6 of 8] mice treated with ¹³¹I-IMP-R4-hRS7, and in 1 of 11 mice treated with ¹³¹I-hRS7(CT). ¹³¹I-IMP-R4-hRS7 was significantly more

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efficacious than 131I-hRS7 (CT) [P = 0.01 for AUC] and the control 131I-IMP-R4-MAb. Conclusion. 131I-IMP-R4-hRS7 is a promising new agent for RAIT, providing significant therapeutic advantage in comparison to the conventionally 131I-labeled antibody.

L22 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2003:980784 HCAPLUS
DOCUMENT NUMBER: 140:47476
TITLE: Stable **radioiodine** conjugates and methods for their synthesis
INVENTOR(S): **Govindan, Serengulam V.**
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: U.S., 13 pp., Cont.-in-part of U.S. 6,558,669.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6663866	B1	20031216	US 2000-605873	20000629
US 6558669	B1	20030506	US 1997-919477	19970828
EP 1219307	A2	20020703	EP 2002-75560	19971219
EP 1219307	A3	20040121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
WO 2002002150	A2	20020110	WO 2001-US20764	20010629
WO 2002002150	C1	20030116		
WO 2002002150	A3	20020906		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1299129	A2	20030409	EP 2001-950673	20010629
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003220470	A1	20031127	US 2003-359276	20030206
US 2004018148	A1	20040129	US 2003-395718	20030325
US 2004022725	A1	20040205	US 2003-411370	20030411
PRIORITY APPLN. INFO.:				
			US 1996-24738P	P 19960828
			US 1997-919477	A2 19970828
			WO 1997-US14998	A 19970827
			EP 1997-954212	A3 19971219
			WO 1997-US23711	A 19971219
			US 2000-605873	A 20000629
			US 2000-696740	A2 20001026
			WO 2001-US20764	W 20010629

APPL.

AB Methods are described for conjugating **radioiodinated** peptides to non-metabolizable carbohydrates with improved yields and qualities of conjugates. **Radioiodinated** residualizing

Searcher : Shears 571-272-2528

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antibody conjugates comprising a carbohydrate-appended peptide are also provided. The instant **radioiodinated** residualizing antibody conjugates are particularly stable in vivo and are suitable for radioimmunoassay and radioimmunotherapy of tumors.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:931008 HCAPLUS

DOCUMENT NUMBER: 140:8761

TITLE: Methods for the purification of stable **radioiodine** conjugates

INVENTOR(S): Govindan, Sergenulam V.

PATENT ASSIGNEE(S): Immunomedics, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S. Ser. No. 696,740.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003220470	A1	20031127	US 2003-359276	20030206
WO 9808548	A2	19980305	WO 1997-US14998	19970827
WO 9808548	A3	19980423		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6558669	B1	20030506	US 1997-919477	19970828
WO 9911294	A1	19990311	WO 1997-US23711	19971219
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
EP 1219307	A2	20020703	EP 2002-75560	19971219
EP 1219307	A3	20040121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6663866	B1	20031216	US 2000-605873	20000629
PRIORITY APPLN. INFO.:				
			US 1996-24738P	P 19960828
			WO 1997-US14998	A 19970827
			US 1997-919477	A2 19970828

APPL.

10/686436

WO 1997-US23711 A 19971219
US 2000-605873 A2 20000629
US 2000-696740 A2 20001026
EP 1997-954212 A3 19971219

AB The present invention relates to the purification of reagents used in radioimmunoassay and radioimmunotherapy and specifically to the purification of **radioiodine** labeled conjugates having enhanced stability in vivo and enhanced retention at tumor sites. It is directed toward a method for preparing and purifying a conjugate of a **radioiodinated** aminopolycarboxylate-appended peptide and a targeting agent. The method involves (A) providing a solution comprising (i) unbound **radioiodine** (ii) a **radioiodinated** aminopolycarboxylate-appended peptide that is not conjugated to a targeting agent (iii) and a **radioiodinated** aminopolycarboxylate-appended peptide that is conjugated to the targeting agent; (B) contacting the solution with an anion-exchange resin; and (C) passing the anion-exchange resin and solution together through a filter capable of trapping anion-exchange resin particles.

L22 ANSWER 4 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2003:265963 BIOSIS

DOCUMENT NUMBER: PREV200300265963

TITLE: Stable **radioiodine** conjugates and methods for their synthesis.

AUTHOR(S): Govindan, Serengulam V. [Inventor, Reprint Author]; Griffiths, Gary L. [Inventor]

CORPORATE SOURCE: ASSIGNEE: Immunomedics, Inc.

PATENT INFORMATION: US 6558669 May 06, 2003

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (May 6 2003) Vol. 1270, No. 1. <http://www.uspto.gov/web/menu/patdata.html>. e-file.

ISSN: 0098-1133 (ISSN print).

DOCUMENT TYPE: Patent

LANGUAGE: English

ENTRY DATE: Entered STN: 4 Jun 2003

Last Updated on STN: 4 Jun 2003

AB Methods are described for conjugating **radioiodinated** peptides or carbohydrate structures to proteins with improved yields and qualities of conjugates. In one method, specially designed **radioiodinated** bifunctional peptides containing nonmetabolizable amide bonds are coupled to antibodies. In a second method, **radioiodinated** nonmetabolizable bifunctional peptides, which also contain aminopolycarboxylates, are coupled to antibodies. In a third method, **radioiodinated** bifunctional aminopolycarboxylates are coupled to antibodies. In a fourth method, a hydrazide-appended antibody is coupled to a **radioiodinated** carbohydrate or a thiolated antibody is coupled to a hydrazide-appended and **radioiodinated** carbohydrate. In a fifth method a monoderivatized cyanuric chloride is used to conjugate thiolated antibody. **Radioiodinated** residualizing antibody conjugates made by these methods are particularly stable in vivo and are suitable for radioimmunoassay and radioimmunotherapy.

Searcher : Shears 571-272-2528

L22 ANSWER 5 OF 29 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

ACCESSION NUMBER: 2004:51001 SCISEARCH

THE GENUINE ARTICLE: 756LU

TITLE: Residualizing **radioiodine**-labeled MAb for therapy of colon cancer: A new radioimmunotherapeutic.

AUTHOR: Stein R (Reprint); Von Govindan S; Chen S; Rosario A; Andrews P; **Griffiths G**; Hansen H J; Horak I D; Goldenberg D M

CORPORATE SOURCE: Garden State Canc Ctr, Belleville, NJ USA; Immunomed Inc, Morris Plains, NJ USA

COUNTRY OF AUTHOR: USA

SOURCE: CLINICAL CANCER RESEARCH, (1 DEC 2003) Vol. 9, No. 16, Part 2, Supp. [S], pp. 6190S-6191S.
Publisher: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA.
ISSN: 1078-0432.

DOCUMENT TYPE: Conference; Journal

LANGUAGE: English

REFERENCE COUNT: 0

L22 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2003:39624 HCAPLUS

DOCUMENT NUMBER: 139:210070

TITLE: Improved Iodine Radiolabels for Monoclonal Antibody Therapy

AUTHOR(S): Stein, Rhona; **Govindan, Serengulam V.**; Mattes, M. Jules; Chen, Susan; Reed, Linda; Newsome, Guy; McBride, Bill J.; **Griffiths, Gary L.**; Hansen, Hans J.; Goldenberg, David M.

CORPORATE SOURCE: Garden State Cancer Center, Belleville, NJ, 07109, USA

SOURCE: Cancer Research (2003), 63(1), 111-118
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A major disadvantage of ¹³¹I-labeled monoclonal antibodies (MAbs) for radioimmunotherapy has been the rapid diffusion of iodotyrosine from target cells after internalization and catabolism of the **radioiodinated** MAbs. We recently reported that a **radioiodinated**, diethylenetriaminepentaacetic acid-appended peptide, designated immunomedics' residualizing peptide 1 (IMP-R1), was a residualizing iodine label that overcame many of the limitations that had impeded the development of residualizing iodine for clin. use. To determine the factors governing the therapeutic index of the labeled MAb, as well as the factors required for production of **radioiodinated** MAb in high yield and with high specific activity, variations in the peptide structure of IMP-R1 were evaluated. A series of **radioiodinated**, diethylenetriaminepentaacetic acid-appended peptide moieties (IMP-R1 through IMP-R8) that differed in overall hydrophilicity and charge were compared. **Radioiodinations** of the peptides followed by conjugations to disulfide-reduced RS7 (an anti-epithelial

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glycoprotein-1 MAb) furnished radioimmunoconjugates in good overall incorporations, with immunoreactivities comparable to that of directly **radioiodinated** RS7. Specific activities of up to 8 mCi/mg and yields > 80% have been achieved. In vitro processing expts. showed marked increases in **radioiodine** retention with all of the adducts; **radioiodine** retention at 45 h was up to 86% greater in cells than with directly iodinated RS7. Each of the 125I-peptide-RS7 conjugates was compared with 131I-RS7 (labeled by the chloramine-T method) in paired-label biodistribution studies in nude mice bearing human lung tumor xenografts. All of the residualizing substrates exhibited significantly enhanced retention in tumor in comparison to directly **radioiodinated** RS7, but the nontarget uptakes differed significantly among the residualizing labels. The best labels were IMP-R4 and IMP-R8, showing superior tumor-to-non-tumor ratios by virtue of high tumor uptake and retention and low normal organ uptake, as well as superior radiochem. properties. The therapeutic efficacy of 131I-IMP-R4-RS7 was compared with that of conventionally 131I-labeled RS7 and 90yttrium-RS7 in the nude mice lung cancer model. The therapeutic efficacy of 131I-IMP-R4-RS7 and 90yttrium-RS7 were equivalent, and both agents yielded significantly improved control of tumor growth compared with conventional 131I-labeled RS7.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L22 ANSWER 7 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on
STN

ACCESSION NUMBER: 2003:370786 BIOSIS
DOCUMENT NUMBER: PREV200300370786
TITLE: A simplified one-pot preparation and purification
method for labeling an anti-CEA MAB, hMN-14, with a
residualizing form of 131I.
AUTHOR(S): Govindan, S. V. [Reprint Author];
Griffiths, G. L.; Andrews, P.; Hansen, H. J.;
Horak, I.; Goldenberg, D. M.
CORPORATE SOURCE: Research, Immunomedics, Inc., Morris Plains, NJ, USA
SOURCE: Journal of Nuclear Medicine, (May 2003) Vol. 44, No.
5 Supplement, pp. 100P. print.
Meeting Info.: 50th Annual Meeting of the Society of
Nuclear Medicine. New Orleans, LA, USA. June 21-25,
2003. Society of Nuclear Medicine.
ISSN: 0161-5505 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Aug 2003
Last Updated on STN: 13 Aug 2003

L22 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2002:31289 HCAPLUS
DOCUMENT NUMBER: 136:107479
TITLE: Stable **radioiodine** conjugates and
methods for their synthesis
INVENTOR(S): Govindan, Serengulam V.

Searcher : Shears 571-272-2528

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PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002002150	A2	20020110	WO 2001-US20764	20010629
WO 2002002150	C1	20030116		
WO 2002002150	A3	20020906		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6663866	B1	20031216	US 2000-605873	20000629
EP 1299129	A2	20030409	EP 2001-950673	20010629

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.:

US 2000-605873	A	20000629
US 1996-24738P	P	19960828
US 1997-919477	A2	19970828
WO 2001-US20764	W	20010629

AB Methods are described for conjugating **radioiodinated** peptides to non-metabolizable carbohydrates with improved yields and qualities of conjugates. **Radioiodinated** residualizing antibody conjugates comprising a carbohydrate-appended peptide are also provided. The instant **radioiodinated** residualizing antibody conjugates are particularly stable in vivo and are suitable for radioimmunodetection and radioimmunotherapy.

L22 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:306823 HCAPLUS

DOCUMENT NUMBER: 139:334838

TITLE: Radiolabeled conjugates for direct and pretargeted radioimmunotherapy

AUTHOR(S): Govindan, S. V.; Griffiths, G. L.; Hansen, H. J.; Goldenberg, D. M.

CORPORATE SOURCE: Immunomedics, Inc., Morris Plains, NJ, 07950, USA

SOURCE: Recent Research Developments in Bioconjugate Chemistry (2002), 1, 1-13
CODEN: RRDBEO

PUBLISHER: Transworld Research Network

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Targeted radiotherapy of cancer via tumor-specific antibodies necessitates the design of optimally performing radiolabeled conjugates whose preparation must be efficient. Very stable

Searcher : Shears 571-272-2528

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radiometalations of monoclonal antibodies using simple and expeditious procedures, methods to introduce intracellularly-stable **radioiodine**, and the syntheses of special low mol. mass haptens for pretargeting strategies are some of the recent advances made in this regard. These current trends in radiolabeling chemistries of bioconjugates are illustrated with examples taken from research at the authors' institutions.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 10 OF 29 SCISEARCH . COPYRIGHT 2004 THOMSON ISI on STN

ACCESSION NUMBER: 2001:485438 SCISEARCH

THE GENUINE ARTICLE: 439XN

TITLE: Radioimmunotherapy of a human lung cancer xenograft with monoclonal antibody RS7: Evaluation of Lu-177 and comparison of its efficacy with that of Y-90 and residualizing I-131

AUTHOR: Stein R (Reprint); Govindan S V; Chen S; Reed L; Richel H; Griffiths G L; Hansen H J; Goldenberg D M

CORPORATE SOURCE: Garden State Canc Ctr, 520 Belleville Ave, Belleville, NJ 07109 USA (Reprint); Garden State Canc Ctr, Belleville, NJ 07109 USA; Immunomed Inc, Morris Plains, NJ USA

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF NUCLEAR MEDICINE, (JUN 2001) Vol. 42, No. 6, pp. 967-974.
Publisher: SOC NUCLEAR MEDICINE INC, 1850 SAMUEL MORSE DR, RESTON, VA 20190-5316 USA.
ISSN: 0161-5505.

DOCUMENT TYPE: Article; Journal

LANGUAGE: English

REFERENCE COUNT: 38

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Tumor targeting and therapeutic efficacy of Lu-177-labeled monoclonal antibody (mAb) RS7 (antiepithelial glycoprotein-1) was evaluated in a human nonsmall cell lung carcinoma xenograft model. The potential of Lu-177-labeled RS7 was compared with that of RS7 labeled with Y-90 and a residualizing form of I-131. Methods: A 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) conjugate of RS7 was used for radiolabeling with Lu-177-acetate or Y-88/90-acetate. Biodistribution and therapy studies were conducted in nude mice with subcutaneous Calu-3 xenografts. Therapy studies were performed using the maxima[tolerated doses (MTDs) of Y-90-DOTA-RS7 (3.9 MBq [105 mu Ci]) and Lu-177-DOTA-RS7 (10.2 MBq [275 mu Ci]) and compared with the data obtained using the MTD (13.0 MBq [350 mu Ci]) of a residualizing form of I-131-RS7. Results: Radiolabeling of RS7-DOTA conjugate with Lu-177-acetate was facile. Lu-177-DOTA-RS7 displayed biodistribution results that were nearly identical to that of the Y-88 analog in a paired-label study. The mean percentage injected doses per gram (%ID/g) for Lu-177-RS7 and Y-88-RS7 (in parentheses) in tumor were 38.3 %ID/g (39.1 %ID/g), 63.0 %ID/g (66.0 %ID/g), 63.0 %ID/g (65.8 %ID/g), and 34.0 %ID/g (34.9 %ID/g) on days 1, 3, 7, and 14, respectively. Elimination of established tumors, with an initial mean tumor volume of 0.24 cm(3).

was shown using doses of Lu-177-DOTA-RS7 ranging from 5.6 to 9.3 MBq (150-250 μ Ci) per nude mouse, with no significant difference in response rate noted between the doses in this range. Specificity of the therapeutic effect was shown in an isotype-matched control experiment, in which Lu-177-DOTA-RS7 was markedly more effective than the (LU)-L-177-DOTA control antibody. A comparison of the therapeutic efficacies of Lu-177-DOTA-RS7 and Y-90-DOTA-RS7, using mice with established tumors with an initial mean tumor volume of 0.85 cm³, indicated similar tumor growth inhibition and similar tumor regrowth profiles. The therapy data were similar to those obtained with residualizing I-131-RS7 obtained at the same time. Conclusion: Lu-177-RS7 is an effective radioimmunoconjugate for radioimmunotherapy. With its radiophysical properties similar to those of I-131, coupled with its facile and stable attachment to mAb, Lu-177 promises to be an alternative to I-131, and a complement to Y-90, in radioimmunotherapy.

L22 ANSWER 11 OF 29 MEDLINE on STN DUPLICATE 5
 ACCESSION NUMBER: 2002022221 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 11418314
 TITLE: Successful therapy of a human lung cancer xenograft using MAb RS7 labeled with residualizing **radioiodine**.
 AUTHOR: Stein R; Govindan S V; Chen S; Reed L; Spiegelman H; Griffiths G L; Hansen H J; Goldenberg D M
 CORPORATE SOURCE: Garden State Cancer Center, 520 Belleville Avenue, Belleville, NJ 07109, USA.. rstein.gscancer@att.net
 CONTRACT NUMBER: CA60039 (NCI)
 SOURCE: CA72324 (NCI)
 SOURCE: Critical reviews in oncology/hematology, (2001 Jul-Aug) 39 (1-2) 173-80.
 Journal code: 8916049. ISSN: 1040-8428.
 PUB. COUNTRY: Ireland
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200112
 ENTRY DATE: Entered STN: 20020121
 Last Updated on STN: 20020121
 Entered Medline: 20011214

AB We have recently reported that a **radioiodinated**, DTPA-appended peptide, designated IMP-R1, is a residualizing iodine label that overcomes many of the limitations that have impeded the development of residualizing iodine for clinical use. In this study the potential of ¹³¹I-IMP-R1-RS7, an internalizing anti-EGP-1 monoclonal antibody, was evaluated by performing preclinical therapy studies in nude mice bearing Calu-3 human non-small cell carcinoma of the lung xenografts. Elimination of 6 of 9 established tumors (mean tumor volume=0.3 cm³) was observed using a single dose of 350 microCi/mouse of ¹³¹I-IMP-R1-RS7, with all animals tolerating the dose. At the same dose and specific activity of ¹³¹I-RS7, labeled using the conventional chloramine-T method, there were four deaths, and one complete remission in nine treated mice. At the maximum tolerated dose of conventionally ¹³¹I-labeled RS7, 275 microCi, mean stable disease for approximately 5 weeks was observed,

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with no complete responses. Specificity of the therapeutic effect was shown in an isotype-matched control experiment, where ¹³¹I-IMP-R1-RS7 was markedly more effective than the (131)I-IMP-R1-labeled control antibody. These studies demonstrate that (131)I-IMP-R1-RS7 provides a therapeutic advantage in comparison to conventional ¹³¹I-labeled RS7, as predicted by the increased tumor accretion observed previously in targeting studies. A direct comparison of the maximum tolerated doses of (131)I-IMP-R1-RS7 (350 microCi) and 90Y-DOTA-RS7 (105 microCi) was performed in this tumor model using large established tumors (mean tumor volume=0.85 cm(3)). Anti-tumor efficacy and toxicity of the two treatments were comparable.

L22 ANSWER 12 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:369599 BIOSIS
DOCUMENT NUMBER: PREV200100369599
TITLE: Improved internalizing **radioiodinated** monoclonal antibodies for therapy.
AUTHOR(S): Stein, Rhona [Reprint author]; **Govindan, Serengulam V.**; Mattes, M. Jules; **Griffiths, Gary L.**; Hansen, Hans J.; Goldenberg, David M.
CORPORATE SOURCE: Garden State Cancer Center, Bellville, NJ, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 93. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research. New Orleans, LA, USA. March 24-28, 2001. American Association for Cancer Research.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 2001
Last Updated on STN: 19 Feb 2002

L22 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 1999:184160 HCAPLUS
DOCUMENT NUMBER: 130:219927
TITLE: Stable **radioiodine** conjugates and methods for their synthesis
INVENTOR(S): **Govindan, Serengulam V.**;
Griffiths, Gary L.
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911294	A1	19990311	WO 1997-US23711	19971219
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,				

Searcher : Shears 571-272-2528

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DE, DK, EE, ES, FI, GB, GE, GM, GW, HU, ID, IL, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,
MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
US 6558669 B1 20030506 US 1997-919477 19970828
CA 2302524 AA 19990311 CA 1997-2302524 19971219
AU 9858050 A1 19990322 AU 1998-58050 19971219
EP 1024838 A1 20000809 EP 1997-954212 19971219
EP 1024838 B1 20020710
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,
PT, IE, FI
JP 2001514236 T2 20010911 JP 2000-508395 19971219
EP 1219307 A2 20020703 EP 2002-75560 19971219
EP 1219307 A3 20040121
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,
PT, IE, FI
AT 220336 E 20020715 AT 1997-954212 19971219
ES 2178042 T3 20021216 ES 1997-954212 19971219
US 2003220470 A1 20031127 US 2003-359276 20030206
PRIORITY APPLN. INFO.:
US 1997-919477 A2 19970828
US 1996-24738P P 19960828
WO 1997-US14998 A 19970827
EP 1997-954212 A3 19971219
WO 1997-US23711 W 19971219
US 2000-605873 A2 20000629
US 2000-696740 A2 20001026

AB Methods are described for conjugating **radioiodinated** peptides or carbohydrate structures to proteins with improved yields and qualities of conjugates. In one method, specially designed **radioiodinated** bifunctional peptides containing nonmetabolizable bonds such as amide bonds are coupled to cell targeting protein. In a second method, **radioiodinated** nonmetabolizable bifunctional peptides, which also contain aminopolycarboxylates, are coupled to protein. In a third method, **radioiodinated** bifunctional aminopolycarboxylates are coupled to protein. In a fourth method, a hydrazide-appended protein is coupled to a **radioiodinated** carbohydrate or a thiolated protein is coupled to a hydrazide-appended and **radioiodinated** carbohydrate. In a fifth method a monoderivatized cyanuric chloride is used to conjugate thiolated protein. **Radioiodinated** residualizing protein conjugates made by these methods are particularly stable in vivo and are suitable for radioimmunodetection and radioimmunotherapy.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 14 OF 29 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2000007360 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10541347
TITLE: Targeting human cancer xenografts with monoclonal antibodies labeled using **radioiodinated**,

Searcher : Shears 571-272-2528

10/686436

AUTHOR: diethylenetriaminepentaacetic acid-appended peptides.
Stein R; Govindan S V; Mattes M J; Shih L
B; Griffiths G L; Hansen H J; Goldenberg D
M
CORPORATE SOURCE: Garden State Cancer Center, Belleville, New Jersey
07109, USA.
CONTRACT NUMBER: CA39841 (NCI)
CA60039 (NCI)
CA72324 (NCI)
SOURCE: Clinical cancer research : an official journal of the
American Association for Cancer Research, (1999 Oct)
5 (10 Suppl) 3079s-3087s.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991124

AB A new nonmetabolizable peptide approach to the production of residualizing **radioiodine** was evaluated in nude mice bearing xenografts of human lung adenocarcinoma (Calu-3) and B-cell lymphoma (Ramos). Monoclonal antibodies (MAbs) RS7 (anti-epithelial glycoprotein-1) and LL2 (anti-CD22) were **radioiodinated** using the thiol-reactive diethylenetriaminepentaacetic acid-D-peptide adducts IMP-R1 and IMP-R2. 125I-IMP-R1- and 125I-IMP-R2-labeled MAbs were compared to the MAbs iodinated by the conventional chloramine-T approach, (111)In, and 131I-dilactitoltyramine (DLT). In vivo biodistribution studies demonstrated a significant improvement in the tumor accretion of radiolabel using the 125I-IMP-R1 labeled MAbs compared with the conventionally iodinated antibodies. For example, at day 7, the percentage of injected dose per gram of tissue in Calu-3 was 7.9 +/- 4.1% and 18.1 +/- 7.9% (P < 0.05) for the conventional 131I- and 125I-IMP-R1-RS7, respectively, and tumor:nontumor ratios were 2.6-4.5-fold higher with the 125I-IMP-R1-RS7. It is estimated that 131I-IMP-R1-RS7 would deliver a dose to tumor (at the estimated maximum tolerated dose) 3.9 times greater than conventional 131I-labeled RS7, 1.4 times greater than 90Y-labeled RS7, and 0.7 times that of 131I-DLT-labeled RS7. Tumor accretion of 125I-IMP-R2-RS7 was also improved compared with conventionally iodinated antibody. However, this label also caused a large increase in kidney accretion. Similar improvements in tumor accretion and tumor:nontumor ratios were observed when 125I-IMP-R1-LL2 was used in the Ramos model. IMP-R1 offers a practical and useful residualizing **radioiodine** label because labeling efficiency is at least 10 times greater than that of the residualizing label DLT, without MAb aggregation. Structural modifications can be envisioned for further improvements in **radioiodine** incorporation, specific activity, and tumor dosimetry, and efforts along these lines are under way.

L22 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:740238 HCAPLUS

Searcher : Shears 571-272-2528

10/686436

DOCUMENT NUMBER: 132:218942
TITLE: Targeting human cancer xenografts with
monoclonal antibodies labeled using
radioiodinated,
diethylenetriaminepentaacetic acid-appended
peptides
AUTHOR(S): Stein, Rhona; Govindan, Serengulam V.;
Jules, Mattes, M.; Shih, Lisa B.;
Griffiths, Gary L.; Hansen, Hans J.;
Goldenberg, David M.
CORPORATE SOURCE: Garden State Cancer Center, Belleville, NJ,
07109, USA
SOURCE: Clinical Cancer Research (1999), 5(10, Suppl.),
3079s-3087s
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new nonmetabolizable peptide approach to the production of residualizing **radioiodine** was evaluated in nude mice bearing xenografts of human lung adenocarcinoma (Calu-3) and B-cell lymphoma (Ramos). Monoclonal antibodies (MAbs) RS7 (anti-epithelial glycoprotein-1) and LL2 (anti-CD22) were **radioiodinated** using the thiol-reactive diethylenetriaminepentaacetic acid-D-peptide adducts IMP-R1 and IMP-R2. 125I-IMP-R1- and 125I-IMP-R2-labeled MAbs were compared to the MAbs iodinated by the conventional chloramine-T approach, 111In, and 131I-dilactitoltyramine (DLT). In vivo biodistribution studies demonstrated a significant improvement in the tumor accretion of radiolabel using the 125I-IMP-R1 labeled MAbs compared with the conventionally iodinated antibodies. For example, at day 7, the percentage of injected dose per g of tissue in Calu-3 was $7.9 \pm 4.1\%$ and $18.1 \pm 7.9\%$ ($P < 0.05$) for the conventional 131I- and 125I-IMP-R1-RS7, resp., and tumor:nontumor ratios were 2.6-4.5-fold higher with the 125I-IMP-R1-RS7. It is estimated that 131I-IMP-R1-RS7 would deliver a dose to tumor (at the estimated maximum tolerated dose) 3.9 times greater than conventional 131I-labeled RS7, 1.4 times greater than 90Y-labeled RS7, and 0.7 times that of 131I-DLT-labeled RS7. Tumor accretion of 125I-IMP-R2-RS7 was also improved compared with conventionally iodinated antibody. However, this label also caused a large increase in kidney accretion. Similar improvements in tumor accretion and tumor:nontumor ratios were observed when 125I-IMP-R1-LL2 was used in the Ramos model. IMP-R1 offers a practical and useful residualizing **radioiodine** label because labeling efficiency is at least 10 times greater than that of the residualizing label DLT, without MAb aggregation. Structural modifications can be envisioned for further improvements in **radioiodine** incorporation, specific activity, and tumor dosimetry, and efforts along these lines are under way.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L22 ANSWER 16 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 1999:90010 HCAPLUS
DOCUMENT NUMBER: 130:334689

Searcher : Shears 571-272-2528

10/686436

TITLE: Labeling of Monoclonal Antibodies with
Diethylenetriaminepentaacetic Acid-Appended
Radioiodinated Peptides Containing
D-Amino Acids

AUTHOR(S): Govindan, Serengulam V.; Mattes, M.
Jules; Stein, Rhona; McBride, Bill J.; Karacay,
Habibe; Goldenberg, David M.; Hansen, Hans J.;
Griffiths, Gary L.

CORPORATE SOURCE: Immunomedics Inc., Morris Plains, NJ, 07950, USA

SOURCE: Bioconjugate Chemistry (1999), 10(2), 231-240
CODEN: BCCHE; ISSN: 1043-1802

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The optimal use of **radioiodinated** internalizing monoclonal antibodies (mAbs) for radio-immunotherapy necessitates the development of practical methods for increasing the level of retention of ¹³¹I in the tumor. Lysosomally trapped ("residualizing") iodine radiolabels that have been previously designed are based mostly on carbohydrate-tyramine adducts, but these methods have drawbacks of low overall yields and/or high levels of mAb aggregation. We have developed a method using thiol-reactive diethylenetriaminepentaacetic acid (DTPA)-peptide adducts wherein the peptides are assembled with one or more D-amino acids, including D-tyrosine. Two such substrates, R-Gly-D-Tyr-D-Lys[1-(p-thiocarbonylamino benzyl)DTPA], referred to as IMP-R1, and [R-D-Ala-D-Tyr-D-Tyr-D-Lys]2(CA-DTPA), referred to as IMP-R2, wherein R is 4-(N-maleimidomethyl)cyclohexane-1-carbonyl, were synthesized by preparing functional group-protected peptides on a solid phase, selectively derivatizing the lysine side chain with 1-(p-isothiocyanatobenzyl)DTPA or DTPA dianhydride (CA-DTPA), deprotecting other functional groups, and finally derivatizing the peptide's N-terminus so it contained a maleimide group. **Radioiodinations** of the peptides followed by conjugations to disulfide-reduced mAbs, carried out as a one-vial procedure, resulted in 32-89% overall yields, at specific activities of 1.8-11.1 mCi/mg, with less than 2% aggregation. Two internalizing mAbs, LL2 (anti-CD 22 B-cell lymphoma mAb) and RS7 (an anti-adenocarcinoma mAb which targets EGP-1 antigen), labeled with this procedure exhibited a 2-3-fold better cellular retention in Ramos and Calu-3 tumor cell lines, in vitro, resp., compared to the same mAbs **radioiodinated** with the chloramine-T method. The rationale for the new approach, syntheses, radiochem. and in vitro data are presented.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L22 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 9

ACCESSION NUMBER: 1998:163486 HCAPLUS

DOCUMENT NUMBER: 128:215069

TITLE: Stable **radioiodinated** peptide and
carbohydrate conjugates with antibodies, and
their preparation, for diagnostic and
therapeutic use

INVENTOR(S): Govindan, Serengulam V.;

Searcher : Shears 571-272-2528

PATENT ASSIGNEE(S): **Griffiths, Gary L.**
 Immunomedics, Inc., USA; Govindan, Serengulam
 V.; Griffiths, Gary L.
 SOURCE: PCT Int. Appl., 42 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 5
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9808548	A2	19980305	WO 1997-US14998	19970827
WO 9808548	A3	19980423		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9743287	A1	19980319	AU 1997-43287	19970827
AU 718859	B2	20000420		
EP 915710	A2	19990519	EP 1997-941363	19970827
EP 915710	B1	20000628		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 194143	E	20000715	AT 1997-941363	19970827
JP 2000517316	T2	20001226	JP 1998-511836	19970827
US 2003220470	A1	20031127	US 2003-359276	20030206
PRIORITY APPLN. INFO.:				
			US 1996-24738P	P 19960828
			WO 1997-US14998	W 19970827
			US 1997-919477	A2 19970828
			WO 1997-US23711	A 19971219
			US 2000-605873	A2 20000629
			US 2000-696740	A2 20001026

AB Methods are described for conjugating **radioiodinated** peptides or carbohydrate structures to proteins with improved yields and qualities of conjugates. In one method, specially designed **radioiodinated** bifunctional peptides containing nonmetabolizable amide bonds are coupled to antibodies. In a second method, **radioiodinated** nonmetabolizable bifunctional peptides, which also contain aminopolycarboxylates, are coupled to antibodies. In a third method, **radioiodinated** bifunctional aminopolycarboxylates are coupled to antibodies. In a fourth method, a hydrazide-appended antibody is coupled to a **radioiodinated** carbohydrate, or a thiolated antibody is coupled to a hydrazide-appended and **radioiodinated** carbohydrate. In a fifth method, a monoderivatized cyanuric chloride is used to conjugate thiolated antibody. **Radioiodinated** residualizing antibody conjugates made by these methods are particularly stable in vivo and are suitable for radioimmunodetection and radioimmunotherapy.

10/686436

L22 ANSWER 18 OF 29 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1998:497454 SCISEARCH
THE GENUINE ARTICLE: ZM639
TITLE: Peptide-based residualizing **radioiodine**
labels for radioimmunotherapy
AUTHOR: **Govindan S V (Reprint)**; Goldenberg D M;
Stein R; Mattes M J; Shih L B; McBride W J; Hansen H
J; **Griffiths G L**
CORPORATE SOURCE: IMMUNOMED INC, MORRIS PLAINS, NJ 07950; GARDEN STATE
CANC CTR, BELLEVILLE, NJ 07109
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF NUCLEAR MEDICINE, (MAY 1998) Vol. 39, No.
5, Supp. [S], pp. 989-989.
Publisher: SOC NUCLEAR MEDICINE INC, 1850 SAMUEL
MORSE DR, RESTON, VA 20190-5316.
ISSN: 0161-5505.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L22 ANSWER 19 OF 29 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on
STN
ACCESSION NUMBER: 1998:337793 BIOSIS
DOCUMENT NUMBER: PREV199800337793
TITLE: Peptide-based residualizing **radioiodine**
labels for radioimmunotherapy.
AUTHOR(S): **Govindan, S. V.** [Reprint author];
Goldenberg, D. M.; Stein, R.; Mattes, M. J.; Shih, L.
B.; McBride, W. J.; Hansen, H. J.; **Griffiths, G.**
L.
CORPORATE SOURCE: Immunomed. Inc., Morris Plains, NJ 07950, USA
SOURCE: Journal of Nuclear Medicine, (May, 1998) Vol. 39, No.
5 SUPPL., pp. 223P. print.
Meeting Info.: 45th Annual Meeting of the Society of
Nuclear Medicine. Toronto, Ontario, Canada. June
7-11, 1998. Society of Nuclear Medicine.
CODEN: JNMEAQ. ISSN: 0161-5505.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Aug 1998
Last Updated on STN: 12 Aug 1998

L22 ANSWER 20 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 1997:439188 HCAPLUS
DOCUMENT NUMBER: 127:132770
TITLE: Advantage of residualizing radiolabels for an
internalizing antibody against the B-cell
lymphoma antigen, CD22
AUTHOR(S): Sharkey, Robert M.; Behr, Thomas M.; Mattes, M.
Jules; Stein, Rhona; **Griffiths, Gary L.**
; Shih, Lisa B.; Hansen, Hans J.; Blumenthal,
Rosalyn D.; Dunn, Robert M.; Juweid, Malik E.;
Goldenberg, David M.

Searcher : Shears 571-272-2528

10/686436

CORPORATE SOURCE: The Garden State Cancer Center, Belleville, NJ,
07109, USA
SOURCE: Cancer Immunology Immunotherapy (1997), 44(3),
179-188
CODEN: CIIMDN; ISSN: 0340-7004
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB LL2 is an anti-CD22 pan-B-cell monoclonal antibody which, when radiolabeled, has a high sensitivity for detecting B-cell, non-Hodgkin's lymphoma (NHL), as well as an antitumor efficacy in therapeutic applications. The aim of this study was to determine whether intracellularly retained radiolabels have an advantage in the diagnosis and therapy of lymphoma with LL2. In vitro studies showed that iodinated LL2 is intracellularly catabolized, with a rapid release of the **radioiodine** from the cell. In contrast, residualizing radiolabels, such as radioactive metals, are retained intracellularly for substantially longer. In vivo studies were performed using LL2-labeled with **radioiodine** by a non-residualizing (chloramine-T) or a residualizing method (dilactitol-tyramine, DLT), or with a radioactive metal (¹¹¹In). The biodistribution of a mixture of ¹²⁵I (non-residualizing chloramine-T compared to residualizing DLT), ¹¹¹In-labeled LL2 murine IgG2a or its fragments [F(ab')₂, Fab'], as well as its humanized, CDR-grafted form, was studied in nude mice bearing the RL human B-cell NHL cell line. Radiation doses were calculated from the biodistribution data according to the Medical International Radiation Dose scheme to assess the potential advantage for therapeutic applications. At all assay times, tumor uptake was higher with the residualizing labels (i.e., ¹¹¹In and DLT-¹²⁵I) than with the non-residualizing iodine label. For example, tumor/blood ratios of ¹¹¹In-labeled IgG were 3.2-, 3.5- and 2.8-fold higher than for non-residualizing iodinated IgG on days 3, 7 and 14, resp. Similar results were obtained for DLT-labeled IgG and fragments with residualized radiolabels. Tumor/organ ratios also were higher with residualizing labels. No significant differences in tumor, blood and organ uptake were observed between murine and humanized LL2. The conventionally iodinated anti-CD20 antibody, 1F5, had tumor uptake values comparable to those of iodinated LL2, the uptake of both antibodies being strongly dependent on tumor size. These data suggest that, with internalizing antibodies such as LL2, labeling with intracellularly retained isotopes has an advantage over released ones, which justifies further clin. trials with residualizing ¹¹¹In-labeled LL2 for diagnosis, and residualizing ¹³¹I and ⁹⁰Y labels for therapy.

L22 ANSWER 21 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 1994:503185 HCAPLUS
DOCUMENT NUMBER: 121:103185
TITLE: Technetium-93m, rhenium-186, and rhenium-188
direct-labeled antibodies
AUTHOR(S): Griffiths, Gary L.; Goldenberg, David
M.; Diril, Habibe; Hansen, Hans J.
CORPORATE SOURCE: Immunomedics, Inc., Morris Plains, NJ, 07103,
USA
SOURCE: Cancer (New York, NY, United States) (1994),

⊙
↓ Nat 3
structures

10/686436

73(3, Suppl.), 761-8
CODEN: CANCAR; ISSN: 0008-543X

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Antibody sulfhydryl groups can act as effective carriers of reduced technetium and rhenium species for radioimmunodetection and radioimmunotherapy. Intact IgG and fragments were labeled with the isotopes and examined in vitro and in vivo. Technetium bound to intact IgG was found to be the most stable species in vitro, but in vivo, clearances of technetium and rhenium bound to intact antibody were similar. Serum clearances were faster than those seen for the corresponding **radioiodinated** antibodies. In vivo clearance rates of the radiolabeled fragments were similar, with kidney uptake and retention seen. Rhenium-labeled antibodies, despite a greater tendency toward in vitro reoxidn. than technetium-labeled antibodies, did not show enhanced kidney clearance in animal models. Rhenium-188 and technetium-99m were obtained from similar generator systems in carrier-free form. Using rhenium-188 spiked with cold rhenium, it was determined that approx. one rhenium atom per mol. of antibody can be conjugated directly. Rhenium-186 also was coupled at almost a 1:1 ratio to antibody. Only radiolysis concerns will limit the amount of rhenium-188 conjugated to antibody. Large doses of antibody will be necessary to deliver rhenium-186 at this isotope's currently available specific activity. Otherwise, higher specific activity rhenium-186, and/or greater loading capacity of rhenium-186 onto antibody, will be needed to generate the type of product that will be usable at a clin. dose of several hundred millicuries.

L22 ANSWER 22 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 12

ACCESSION NUMBER: 1991:119888 HCAPLUS

DOCUMENT NUMBER: 114:119888

TITLE: Differential endocytosis of CD4 in lymphocytic and nonlymphocytic cells

AUTHOR(S): Pelchen-Matthews, Annegret; Armes, Jane E.;
Griffiths, Gareth; Marsh, Mark

CORPORATE SOURCE: Chester Beatty Lab., Inst. Cancer Res., London,
SW3 6JB, UK

SOURCE: Journal of Experimental Medicine (1991), 173(3),
575-87

CODEN: JEMEAV; ISSN: 0022-1007

DOCUMENT TYPE: Journal
LANGUAGE: English

AB The endocytosis of the T cell differentiation antigen CD4 has been investigated in CD4-transfected HeLa cells, the promyelocytic HL-60 cell line, and in a number of leukemia- or lymphoma-derived T cell lines. CD4 internalization was followed using **radioiodinated** antibodies in an acid-elution endocytosis assay, or by covalently modifying cell surface proteins with biotin and analyzing CD4 distributions by immunopptn.; both approaches gave equivalent results. The assays demonstrated that in transfected HeLa cells and in HL-60 cells CD4 was constitutively internalized and recycled in the absence of ligand. Immunogold labeling and electron microscopy demonstrated that CD4 enters cells through coated pin. In contrast to the nonlymphocytic cells, T cell lines showed very little endocytosis of CD4. Measurements of fluid phase endocytosis

and morphometric anal. of the endosome compartment indicated that the endocytic capacities of HeLa and lymphoid cells are equivalent and suggested that the low level of CD4 uptake in lymphocytic cells is due to exclusion of CD4 from coated pits. This conclusion was supported by expts. using truncated CD4 mols., lacking the bulk of the cytoplasmic domain, which were internalized equally efficiently in both transfected lymphocytes and HeLa cells. These results indicate that the cytoplasmic domain of CD4 mediates the different interactions with the endocytic apparatus in lymphoid and nonlymphoid cells. The CD4-associated lymphocyte-specific protein tyrosine kinase p56lck may be involved in preventing CD4 endocytosis in T cells.

L22 ANSWER 23 OF 29 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
 ACCESSION NUMBER: 91:121961 SCISEARCH
 THE GENUINE ARTICLE: EZ663
 TITLE: DIFFERENTIAL ENDOCYTOSIS OF CD4 IN LYMPHOCYTIC AND
 NONLYMPHOCYTIC CELLS
 AUTHOR: PELCHENMATTHEWS A; ARMES J E; GRIFFITHS G;
 MARSH M (Reprint)
 CORPORATE SOURCE: INST CANC RES, CHESTER BEATTY LABS, FULHAM RD,
 LONDON SW3 6JB, ENGLAND; EUROPEAN MOLEC BIOL LAB,
 W-6900 HEIDELBERG, GERMANY
 COUNTRY OF AUTHOR: ENGLAND; GERMANY
 SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1991) Vol. 173,
 No. 3, pp. 575-587.
 DOCUMENT TYPE: Article; Journal
 FILE SEGMENT: LIFE
 LANGUAGE: ENGLISH
 REFERENCE COUNT: 70

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The endocytosis of the T cell differentiation antigen CD4 has been investigated in CD4-transfected HeLa cells, the promyelocytic HL-60 cell line, and in a number of leukemia- or lymphoma-derived T cells lines. CD4 internalization was followed using **radioiodinated** antibodies in an acid-elution endocytosis assay, or by covalently modifying cell surface proteins with biotin and analyzing CD4 distributions by immunoprecipitation; both approaches gave equivalent results. The assays demonstrated that in transfected HeLa cells and in HL-60 cells CD4 was constitutively internalized and recycled in the absence of ligand. Immunogold labeling and electron microscopy demonstrated that CD4 enters cells through coated pits.

In contrast to the nonlymphocytic cells, T cell lines showed very little endocytosis of CD4. Measurements of fluid phase endocytosis and morphometric analysis of the endosome compartment indicated that the endocytic capacities of HeLa and lymphoid cells are equivalent and suggested that the low level of CD4 uptake in lymphocytic cells is due to exclusion of CD4 from coated pits. This conclusion was supported by experiments using truncated CD4 molecules, lacking the bulk of the cytoplasmic domain, which were internalized equally efficiently in both transfected lymphocytes and HeLa cells. Together, these results indicate that the cytoplasmic domain of CD4 mediates the different interactions with the endocytic apparatus in lymphoid and nonlymphoid cells. We suggest that the CD4-associated lymphocyte-specific protein tyrosine kinase p56lck may be involved in preventing CD4 endocytosis in T cells.

L22 ANSWER 24 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 13

ACCESSION NUMBER: 1987:28580 HCAPLUS
 DOCUMENT NUMBER: 106:28580
 TITLE: Identification and quantification of ricin toxin
 in animal tissues using ELISA
 AUTHOR(S): Griffiths, G. D.; Newman, Helen; Gee,
 D. J.
 CORPORATE SOURCE: Dep. Forensic Med., St. James Univ. Hosp.,
 Leeds, LS9 7TF, UK
 SOURCE: Journal of the Forensic Science Society (1986),
 26(5), 349-58
 CODEN: FSSJAS; ISSN: 0015-7368
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB A rapid, relatively inexpensive, reliable, and straightforward method for the demonstration and quantification of ricin in animal tissues following an injection was developed. The use of **radioiodinated** ricin provided an indication as to where the highest levels of toxin might be found; the highly sensitive and specific use of antibodies in ELISA was employed as an alternative to the more expensive and more tedious procedure of RIA. The injection site, lymphoid tissues, and liver contained detectable amts. of the toxin. In cases where administration of ricin was suspected, confirmation using biopsied tissue samples could enable appropriate remedial measures to be taken. Alternatively, in cases of suspicious deaths, postmortem tissues would be used to identify the presence of toxin in the body and could be of significant value to forensic diagnosis. The advantage of this method over that of immunocytochem. is discussed.

L22 ANSWER 25 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 14

ACCESSION NUMBER: 1986:455789 HCAPLUS
 DOCUMENT NUMBER: 105:55789
 TITLE: Immunocytochemical detection of ricin. II.
 Further studies using the immunoperoxidase method
 AUTHOR(S): Griffiths, G. D.; Newman, H. V.; Gee,
 D. J.
 CORPORATE SOURCE: Dep. Forensic Med., St. James's Univ., Leeds,
 LS9 7TF, UK
 SOURCE: Histochemical Journal (1986), 18(4), 189-95
 CODEN: HISJAE; ISSN: 0018-2214
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB **Radioiodinated** ricin was injected into rat muscle in vivo to establish the distribution of the toxin at various time intervals after injection. Injection site muscle and paraaortic lymph nodes were selected for localization of ricin by the immunoperoxidase technique. Sections of snap-frozen tissues were fixed using a variety of methods to establish the best protocol for the immunodetection method. This was found to be with an Et2O-EtOH mixture Ricin was detected in tissue at the site of injection taken from rats sacrificed 1, 4, 8, and 24 h after injection and in tissue from animals dying from ricin intoxication after .apprx.30 h. This method, however, failed to demonstrate unequivocally the presence of

ricin in lymphoid tissue which had been indicated by the radiotracer study. The significance of these findings and their relevance to forensic diagnosis are discussed.

L22 ANSWER 26 OF 29 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 15

ACCESSION NUMBER: 1979:553228 HCAPLUS

DOCUMENT NUMBER: 91:153228

TITLE: **Radioiodination** of chicken erythrocyte histones H4 and H5 in chromatin

AUTHOR(S): **Griffiths, Garth R.**; Huang, P. C.

CORPORATE SOURCE: Sch. Hyg. Public Health, Johns Hopkins Univ., Baltimore, MD, 21205, USA

SOURCE: Journal of Biological Chemistry (1979), 254(16), 8057-66

CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The conformational state of histones in isolated chicken erythrocyte chromatin was studied using procedures developed for probing surface proteins on membranes. Under controlled conditions, only exposed tyrosyl residues react with iodide radicals, generated either by the oxidant, chloramine-T, or the enzyme lactoperoxidase, giving moniodotyrosine. Using I¹²⁵I₂, the reactive tyrosines in free and bound histones H4 and H5 were compared. The relative extent of iodination of these histones within (H4) and outside (H5) of the nucleosomes was measured after extraction and gel electrophoresis. Each of the histones was further analyzed for the extent of specific tyrosine iodination by separating the tryptic peptides by high voltage electrophoresis. The identity of the labeled peptide was determined by dansylation of the amino acids present in each hydrolyzed peptide. There is a difference in the conformational arrangement of these histones on chromatin and in the free forms, since in chromatin not all tyrosine residues are as accessible for iodination as in the denatured state. Residue 53 of histone H5 for instance is more reactive than residues 28 and 58, indicating that the segments containing the latter residues are involved in either protein-DNA or protein-protein interactions. In histone H4, preferential labeling of 2 of the 4 tyrosines present was also observed

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ACCESSION NUMBER: 78387472 EMBASE

DOCUMENT NUMBER: 1978387472

TITLE: Confirmation studies of chick erythrocyte chromatin by **radioiodination**.

AUTHOR: **Griffiths G.R.**; Huang P.C.

CORPORATE SOURCE: Dept. Biochem., Johns Hopkins Univ., Baltimore, Md. 21205, United States

SOURCE: Federation Proceedings, (1978) 37/6 (No.2036).

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DOCUMENT TYPE: Journal

LANGUAGE: English

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ACCESSION NUMBER: 1978:59884 BIOSIS
DOCUMENT NUMBER: PREV197815003384; BR15:3384
TITLE: CONFORMATION STUDIES OF CHICK ERYTHROCYTE CHROMATIN
BY **RADIO IODINATION**.
AUTHOR(S): **GRIFFITHS G R; HUANG P C**
SOURCE: Federation Proceedings, (1978) Vol. 37, No. 6, pp.
1640.
CODEN: FEPR7. ISSN: 0014-9446.
DOCUMENT TYPE: Article
FILE SEGMENT: BR
LANGUAGE: Unavailable

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ACCESSION NUMBER: 78:45316 CONFSCI
DOCUMENT NUMBER: 78087997
TITLE: Conformation studies of chick erythrocyte chromatin
by **radioiodination**.
AUTHOR: **Griffiths, G.R.**
CORPORATE SOURCE: Johns Hopkins Univ.
SOURCE: Abstracts (Eng) in Abstracts Volume (Vol. 37, No.6 of
"Federation Proceedings," 1 May 78) \$12 members or
payment of registration fee plus \$12 to non-members:
Mrs. H. B. Lemp, 9650 Rockville Pike, Bethesda, MD
20014..
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Chemists 69th Annual Meeting/American Association of
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